Settings

Item 1 of 40
Question Id: 1964

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

A 57-year-old male presents to your office complaining of fatigue and low energy. He also notes experiencing intermittent back pain that responds to ibuprofen. He has no significant past medical history. His family history is significant for his father dying of a heart attack at age 60. Fecal occult blood testing is negative. Laboratory studies reveal:

Hematocrit	36%
MCV	86 fl
WBC	7,000/mm^3
Platelets	170,000/mm^3
Sodium	136 mEq/L
Potassium	4.5 mEq/L
AST	34 U/L
ALT	18 U/L
Bilirubin	0.8 mg/dL
Creatinine	2.0 mg/dL

Plasma protein electrophoresis reveals a high peak corresponding to gamma-globulins. The most likely diagnosis is:

A. Iron deficiency
B. Cobalamin deficiency
C. Chronic lymphocytic leukemia

Block Time Remaining: 00:00:03
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10 | Feedback | Suspend | End Block

4:06 PM
2/10/2019

Settings

Item 1 of 40
Question Id: 1964

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

Sodium	136 mEq/L
Potassium	4.5 mEq/L
AST	34 U/L
ALT	18 U/L
Bilirubin	0.8 mg/dL
Creatinine	2.0 mg/dL

Plasma protein electrophoresis reveals a high peak corresponding to gamma-globulins. The most likely diagnosis is:

- A. Iron deficiency
- B. Cobalamin deficiency
- C. Chronic lymphocytic leukemia
- D. Aplastic anemia
- E. Plasma cell neoplasm
- F. Hodgkin lymphoma
- G. Hypothyroidism

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Block Time Remaining: 00:00:05
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10 | Feedback | Suspend | End Block

4:06 PM
2/10/2019

Settings

Item 1 of 40
Question Id: 1964

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

Sodium	136 mEq/L
Potassium	4.5 mEq/L
AST	34 U/L
ALT	18 U/L
Bilirubin	0.8 mg/dL
Creatinine	2.0 mg/dL

Plasma protein electrophoresis reveals a high peak corresponding to gamma-globulins. The most likely diagnosis is:

- A. Iron deficiency [3%]
- B. Cobalamin deficiency [1%]
- C. Chronic lymphocytic leukemia [5%]
- D. Aplastic anemia [3%]
- ✔ E. Plasma cell neoplasm [81%]
- F. Hodgkin lymphoma [2%]
- G. Hypothyroidism [1%]

Omitted
Correct answer

81%
Answered correctly

7 Seconds
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08/27/2018
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2/10/2019

Explanation

In multiple myeloma, neoplastic B-lymphocytes mature into plasma cells that synthesize abnormal (typically large) amounts of monoclonal immunoglobulin or immunoglobulin fragments (e.g. light chains). Clinical manifestations of multiple myeloma include impaired hematopoiesis leading to a normochromic, normocytic anemia and weakness; lytic bone lesions classically affecting the vertebral column and causing back pain and pathologic fractures; and hypercalcemia and AL amyloidosis, which contribute to renal dysfunction. Severe amyloidosis can also cause cardiac and cutaneous findings.

The classic laboratory abnormalities in multiple myeloma include erythrocyte rouleaux formation on peripheral blood smear and Bence-Jones proteins in the urine. Serum protein electrophoresis (SPEP) is a more specific laboratory test used to determine if excessive monoclonal immunoglobulins are present in the serum. An "M peak" on SPEP indicates the presence of such an immunoglobulin. (An M peak may also be found in Waldenstrom macroglobulinemia and some lymphomas.)

(Choices A and B) Iron deficiency can cause weakness due to a hypochromic, microcytic anemia and vitamin B12 (cobalamin) deficiency can cause weakness due to a macrocytic anemia. Vitamin B12 deficiency can also cause neurologic signs.

(Choice C) CLL is a lymphocytic malignancy that may cause a normochromic, normocytic anemia, but immunoglobulin production is classically depressed, not increased, in CLL.

(Choice D) Aplastic anemia would cause a uniform depression of all hematologic cell lines, including leukocytes and platelets.

(Choice F) Hodgkin lymphoma is a B-cell malignancy characterized by the presence of Reed-Sternberg cells on lymph node histology. There may be anemia of chronic disease in patients with this condition, but a monoclonal gammopathy would not be expected.

(Choice G) Patients with hypothyroidism may be anemic due to associated iron deficiency or pernicious anemia. However, monoclonal gammopathy would not be expected.

Educational Objective:
The finding of a high peak in the gamma-globulin region on serum protein electrophoresis (SPEP) usually represents an M protein consisting of an

leading to a normochromic, normocytic anemia and weakness; lytic bone lesions classically affecting the vertebral column and causing back pain and pathologic fractures; and hypercalcemia and AL amyloidosis, which contribute to renal dysfunction. Severe amyloidosis can also cause cardiac and cutaneous findings.

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(Choice G) Patients with hypothyroidism may be anemic due to associated iron deficiency or pernicious anemia. However, monoclonal gammopathy would not be expected.

Educational Objective:
The finding of a high peak in the gamma-globulin region on serum protein electrophoresis (SPEP) usually represents an M protein consisting of an overproduced monoclonal immunoglobulin. Multiple myeloma causes an M protein peak on SPEP as well as anemia (weakness), lytic bone lesions (back pain, pathologic fractures), and renal insufficiency (related to amyloid deposition and hypercalcemia).

Settings

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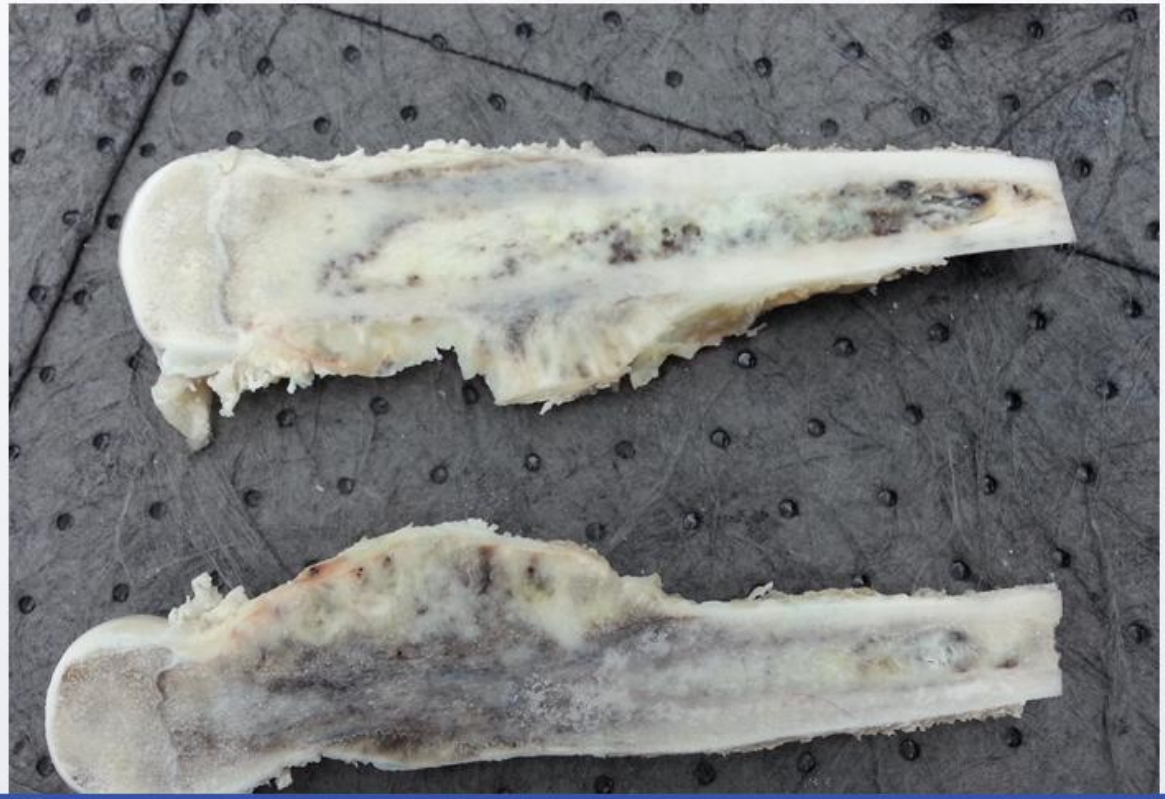
Item 2 of 40
Question Id: 15645

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

An 18-year-old man is evaluated due to 3 months of lower extremity pain. The pain is persistent and present both day and night. He has no fever, chills, or history of leg trauma. Imaging shows an expansile lesion of the distal femur. Surgical resection is performed, and the specimen is shown below.



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2/10/2019

Settings

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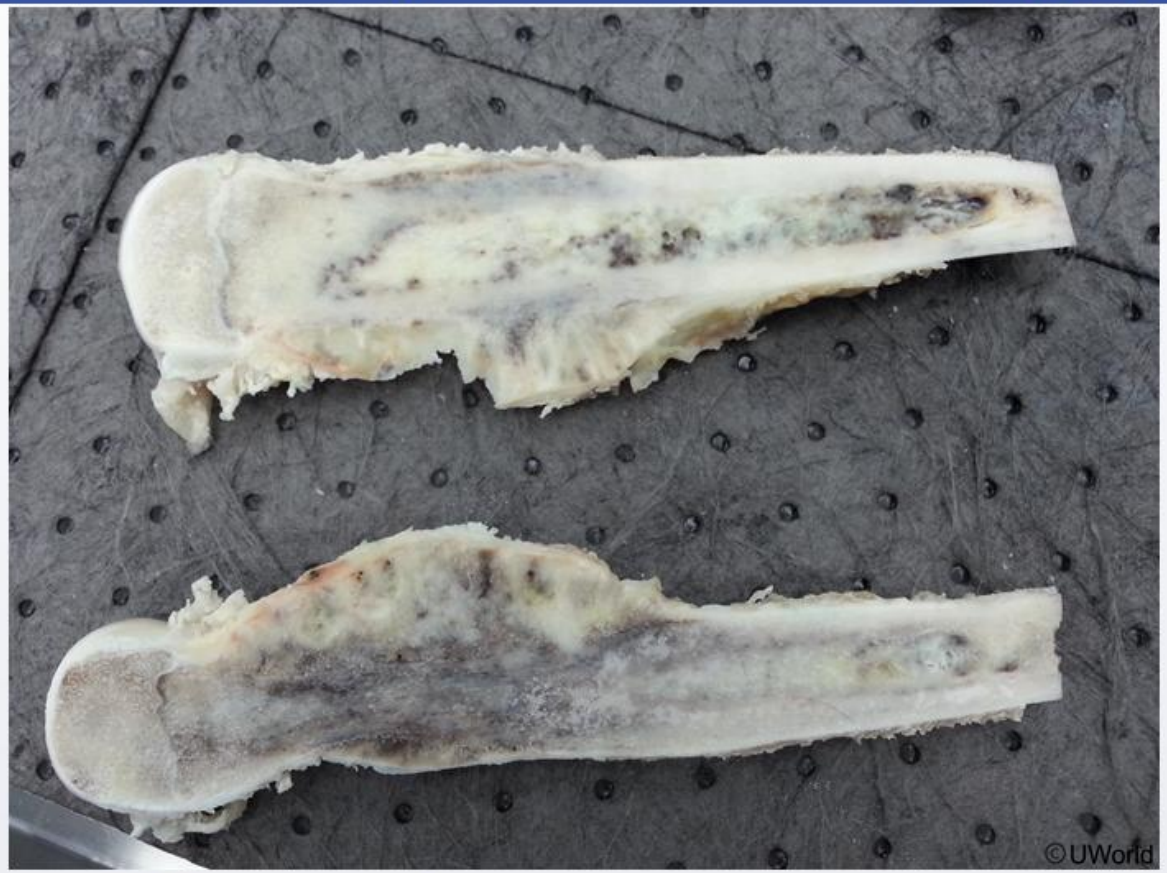
Item 2 of 40
Question Id: 15645

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



Mutations involving which of the following genes are most likely present in this patient?

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4:06 PM
2/10/2019

Settings

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Item 2 of 40
Question Id: 15645

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

Mutations involving which of the following genes are most likely present in this patient?

A. *BRAF*
B. *HER2*
C. *KRAS*
D. *RB1*
E. *RET*

Submit

Block Time Remaining: 00:00:17
TUTOR

10 | Feedback | Suspend | End Block

4:06 PM
2/10/2019

Settings

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28

Item 2 of 40
Question Id: 15645

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

Mutations involving which of the following genes are most likely present in this patient?

A. *BRAF* [8%]
B. *HER2* [0%]
C. *KRAS* [9%]
D. *RB1* [73%]
E. *RET* [7%]

Omitted
Correct answer

73%
Answered correctly

12 Seconds
Time Spent

02/04/2019
Last Updated

Block Time Remaining: 00:00:19
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4:06 PM
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Explanation

Proto-oncogenes 1-hit GAIN of function		Tumor suppressor genes 2-hit LOSS of function	
RAS (GTP-binding protein)	• Cholangiocarcinoma • Pancreatic adenocarcinoma	***BRCA1/2*** (DNA repair genes)	• Breast & ovarian cancer
MYC (Transcription factor)	• Burkitt lymphoma	***APC/β-catenin*** (Wnt signaling pathway)	• Colon, gastric & pancreatic cancer • Familial adenomatous polyposis
ERBB1 (EGFR) (Receptor tyrosine kinase)	• Lung adenocarcinoma	***TP53*** (Genomic stability)	• Most cancers • Li-Fraumeni syndrome
ERBB2 (HER2) (Receptor tyrosine	• Breast cancer	***RB*** (G_1/S transition inhibitor)	• Retinoblastoma • Osteosarcoma

(EGFR) (Receptor tyrosine kinase)	• Lung adenocarcinoma	***TP53*** (Genomic stability)	• Most cancers • Li-Fraumeni syndrome
ERBB2 (HER2) (Receptor tyrosine kinase)	• Breast cancer	***RB*** (G_1/S transition inhibitor)	• Retinoblastoma • Osteosarcoma
ABL (Nonreceptor tyrosine kinase)	• Chronic myelogenous leukemia	***WT1*** (Urogenital differentiation)	• Wilms tumor
BRAF (Ras signal transduction)	• Hairy cell leukemia • Melanoma	***VHL*** (Ubiquitin ligase component)	• Renal cell carcinoma • Von Hippel-Lindau syndrome

This patient's **expansile tumor** in the distal femur likely indicates **osteosarcoma**, the most common primary bone tumor affecting children and **young adults**. Most cases arise at the metaphysis of long bones and present with progressive pain and swelling.

Osteosarcomas typically form when a **mesenchymal stem cell** develops mutations in the following genes:

- ***RB1*** tumor suppressor gene, which encodes for RB, a protein that regulates cell-cycle progression. Inactivating mutations to *RB1* promote

young adults. Most cases arise at the metaphysis of long bones and present with progressive pain and swelling.

Osteosarcomas typically form when a **mesenchymal stem cell** develops mutations in the following genes:

- ***RB1*** tumor suppressor gene, which encodes for RB, a protein that regulates cell-cycle progression. Inactivating mutations to *RB1* promote unchecked and unregulated cellular replication and are associated with osteosarcoma, **retinoblastoma**, melanoma, and soft-tissue sarcomas.
- *TP53* tumor suppressor gene, which encodes for P53, a protein that regulates cell-cycle progression and maintains genomic integrity by activating DNA repair following damage. Germ-line mutations to *TP53* are associated with **Li-Fraumeni syndrome**, which increases the risk for multiple tumors (eg, osteosarcoma, other bone and soft-tissue sarcomas, breast cancer, brain tumors, adrenal carcinomas).

(Choice A) Activating mutations of *BRAF* are responsible for most cases of hairy cell leukemia, a B-cell neoplasm that typically presents in older patients with pancytopenia, splenomegaly, and systemic symptoms (eg, fatigue, recurrent infections). It is also present in many cases of malignant melanoma.

(Choice B) *HER2*, an oncogene encoding for an epidermal growth factor receptor, is amplified or overexpressed in many forms of invasive breast cancer. Treatment of the *HER2* gene product can improve outcomes in these individuals.

(Choice C) Activating mutations in the *KRAS* proto-oncogene are common in colorectal cancer and non-small cell lung cancer. *KRAS* encodes for a GTPase that relays cellular growth and proliferation signals from outside the cell.

(Choice E) Germ-line mutations of the *RET* proto-oncogene cause multiple endocrine neoplasia type 2, which is associated with pheochromocytoma, medullary thyroid cancer, parathyroid hyperplasia, and/or mucosal neuromas.

Educational objective:
Osteosarcoma is the most common primary bone malignancy in children and young adults. It occurs most frequently at the metaphyses of long bones and presents with local pain and swelling. Most cases are associated with sporadic or inherited mutations in *RB1* (hereditary retinoblastoma) and *TP53* (Li-Fraumeni syndrome).

Settings

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Item 2 of 40
Question Id: 15645

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

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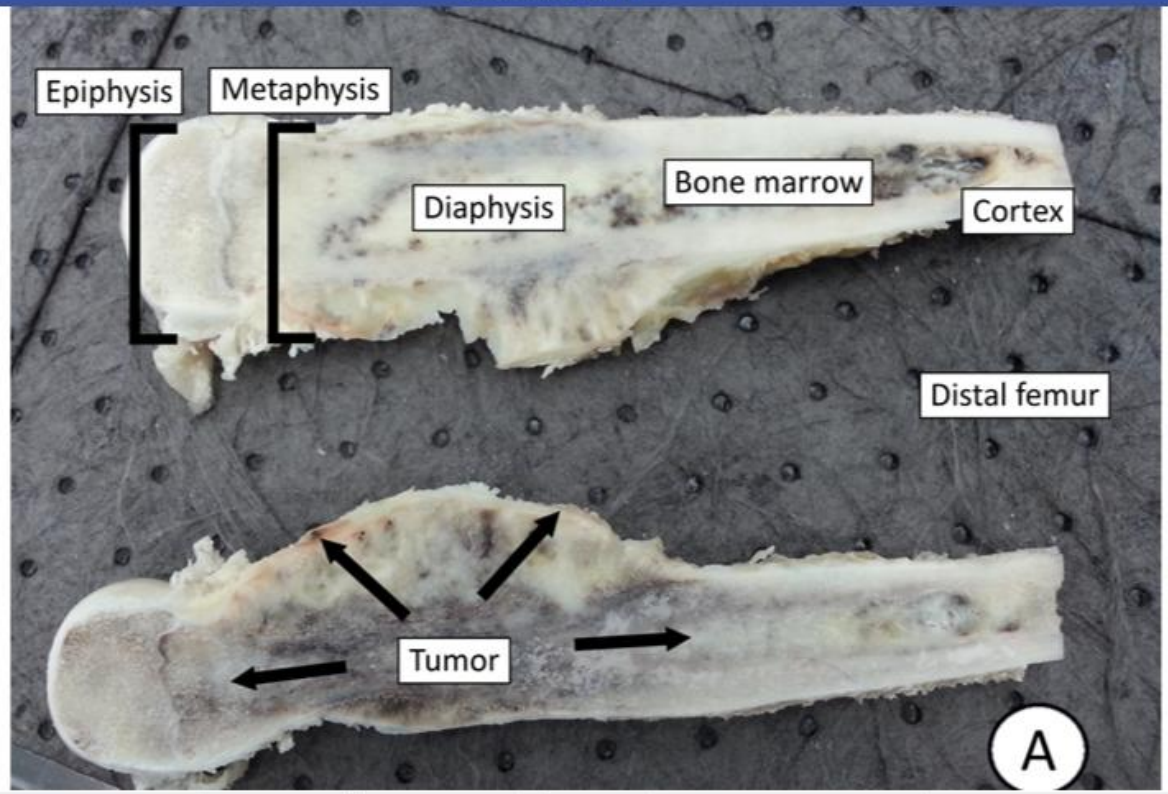

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malignant melanoma.

Block Time Remaining: 00:00:19
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2/10/2019

Settings

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28

Item 3 of 40
Question Id: 895

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

A 2-week-old girl is brought to her primary care provider for a routine visit. The patient was born by normal spontaneous vaginal delivery at 39 weeks gestation. The mother is breastfeeding exclusively, and the infant has regained her birth weight. Newborn screening results from hemoglobin electrophoresis are as follows:

Hemoglobin F	70%
Hemoglobin A	20%
Hemoglobin S	10%

The patient's mother has sickle cell trait, and a maternal cousin has sickle cell anemia. Examination shows a well-appearing infant with no pallor or splenomegaly. Which of the following is most likely true about this patient?

A. Life expectancy will be shorter than average
B. Mean corpuscular volume will be decreased
C. Reticulocyte count will be elevated
D. She has relative protection from *Plasmodium falciparum*
E. She will likely develop pain crises

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Block Time Remaining: 00:00:20
TUTOR

10 | Feedback | Suspend | End Block

4:07 PM
2/10/2019

Settings

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28

Item 3 of 40
Question Id: 895

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

A 2-week-old girl is brought to her primary care provider for a routine visit. The patient was born by normal spontaneous vaginal delivery at 39 weeks gestation. The mother is breastfeeding exclusively, and the infant has regained her birth weight. Newborn screening results from hemoglobin electrophoresis are as follows:

Hemoglobin F	70%
Hemoglobin A	20%
Hemoglobin S	10%

The patient's mother has sickle cell trait, and a maternal cousin has sickle cell anemia. Examination shows a well-appearing infant with no pallor or splenomegaly. Which of the following is most likely true about this patient?

A. Life expectancy will be shorter than average [1%]
B. Mean corpuscular volume will be decreased [2%]
C. Reticulocyte count will be elevated [5%]
✔ D. She has relative protection from *Plasmodium falciparum* [85%]
E. She will likely develop pain crises [4%]

Omitted
Correct answer
D

85%
Answered correctly

3 Seconds
Time Spent

09/27/2018
Last Updated

Block Time Remaining: 00:00:22
TUTOR

10 | Feedback | Suspend | End Block

4:07 PM
2/10/2019

Sickle cell trait	
Clinical features	• Usually no symptoms of sickle cell anemia • More prevalent in African, Middle-Eastern & Mediterranean countries; African American & Hispanic individuals • No change in overall life expectancy
Diagnosis	• Normal hemoglobin, reticulocyte count, RBC indices & morphology • Hemoglobin electrophoresis shows both Hb A & Hb S, with the amount of Hb A greater than Hb S

Hb A = hemoglobin A; **Hb S** = hemoglobin S; **RBC** = red blood cells.

This patient's hemoglobin electrophoresis from her newborn screen is most consistent with **sickle cell trait**. At birth, infants who are **heterozygous** for sickle cell trait typically have the greatest amount of fetal hemoglobin (Hb F), followed by hemoglobin A (Hb A), and the smallest amount of hemoglobin S (Hb S). Hb A continues to be higher than Hb S throughout the lifetime of these patients as **Hb F naturally declines**, offering protection from sickle cell anemia, aplastic crises, and splenic sequestration. Patients with sickle cell trait are usually **asymptomatic** with normal hemoglobin level, reticulocyte count, and red blood cell (RBC) indices. However, they may develop hematuria, priapism, and increased incidence of urinary tract infections. Splenic infarction at high altitudes has also been reported.

Patients with sickle cell trait have **relative protection from *Plasmodium falciparum* (malaria)**, resulting in lower rates of severe malaria and hospitalization than seen in the general population. Possible mechanisms include increased sickling of parasitized sickle cell trait RBCs and

This patient's hemoglobin electrophoresis from her newborn screen is most consistent with **sickle cell trait**. At birth, infants who are **heterozygous** for sickle cell trait typically have the greatest amount of fetal hemoglobin (Hb F), followed by hemoglobin A (Hb A), and the smallest amount of hemoglobin S (Hb S). Hb A continues to be higher than Hb S throughout the lifetime of these patients as **Hb F naturally declines**, offering protection from sickle cell anemia, aplastic crises, and splenic sequestration. Patients with sickle cell trait are usually **asymptomatic** with normal hemoglobin level, reticulocyte count, and red blood cell (RBC) indices. However, they may develop hematuria, priapism, and increased incidence of urinary tract infections. Splenic infarction at high altitudes has also been reported.

Patients with sickle cell trait have **relative protection from *Plasmodium falciparum* (malaria)**, resulting in lower rates of severe malaria and hospitalization than seen in the general population. Possible mechanisms include increased sickling of parasitized sickle cell trait RBCs and accelerated removal of these cells by the splenic monocyte-macrophage system. These patients are not immune to malaria, however, and those visiting malaria-endemic areas should still receive prophylaxis.

(Choice A) Life expectancy of patients with sickle cell trait is no different than that of the general population. Patients who are homozygous for the sickle cell mutation have a decreased life expectancy due to significant complications of disease (eg, acute chest syndrome, infection from encapsulated organisms).

(Choices B and C) Patients with sickle cell trait typically have normal RBC indices and reticulocyte counts. Individuals with sickle cell anemia (eg, no normal Hb A) will have an elevated reticulocyte count but will maintain a normal mean corpuscular volume.

(Choice E) It is unlikely that this patient will develop painful crises as she is protected by the predominance of Hb A (normal hemoglobin) over Hb S. Vaso-occlusive pain crises that develop in patients with sickle cell anemia are thought to occur when Hb S polymerizes and causes the RBCs to assume a sickle shape, typically in response to a trigger (eg, cold weather, dehydration).

Educational objective:
Patients with sickle cell trait are typically asymptomatic and have relative protection from malaria caused by *Plasmodium falciparum*. These patients usually have normal hemoglobin, reticulocyte, and red blood cell index values. Life expectancy is the same as that of the general population.

Exhibit Display

Hemoglobin electrophoresis patterns			
Diagnosis	**Hemoglobin A**	**Hemoglobin S**	**Hemoglobin F**
Normal	~99%	0%	<1%
Sickle cell disease	0%	85-95%	5-15%
Sickle cell trait	50-60%	35-45%	<2%

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incidence of urinary tract infections. Splenic infarction at high altitudes has also been reported.

Settings

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28

Item 4 of 40
Question Id: 12049

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

A 61-year-old man comes to the office due to 4 months of easy fatigability, anorexia, and a 4.5-kg (10-lb) unintentional weight loss. His stool occult blood testing is positive, and laboratory studies show microcytic hypochromic anemia. Colonoscopy reveals a 6-cm (2.4-in) mass in the descending colon. Biopsy samples obtained during the procedure are consistent with adenocarcinoma. A subsequent CT scan of the abdomen shows multiple metastatic liver lesions. Therapy with monoclonal antibodies that bind to epidermal growth factor receptors on the malignant cells is considered. An activating mutation in which of the following will most likely make this therapy ineffective?

A. Adenomatous polyposis coli protein
B. KRAS protein
C. p53 protein
D. Platelet-derived growth factor
E. Vascular endothelial growth factor

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Block Time Remaining: 00:00:23
TUTOR

10 | Feedback | Suspend | End Block

4:07 PM
2/10/2019

Settings

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28

Item 4 of 40
Question Id: 12049

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

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A. Adenomatous polyposis coli protein [6%]
✔ B. KRAS protein [56%]
C. p53 protein [11%]
D. Platelet-derived growth factor [7%]
E. Vascular endothelial growth factor [17%]

Omitted
Correct answer
B

56%
Answered correctly

3 Seconds
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09/06/2018
Last Updated

Explanation

KRAS mutation causing anti-EGFR resistance

Block Time Remaining: 00:00:25
TUTOR

10 | Feedback | Suspend | End Block

4:07 PM
2/10/2019

Settings

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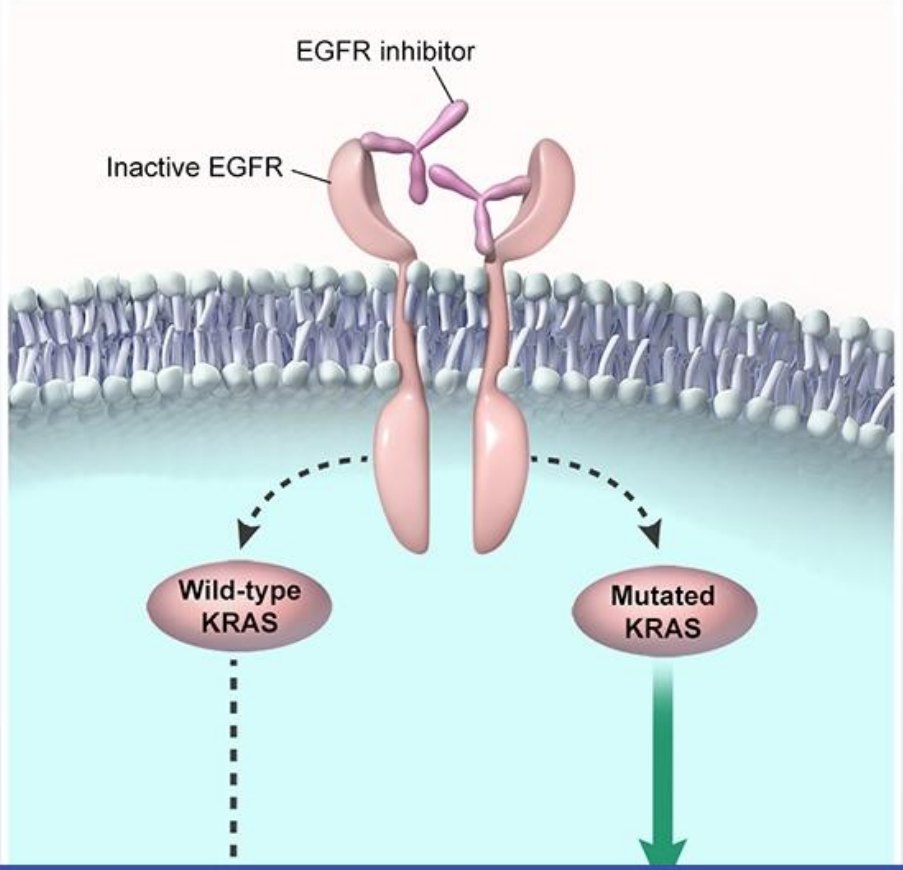
Item 4 of 40
Question Id: 12049

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

KRAS mutation causing anti-EGFR resistance



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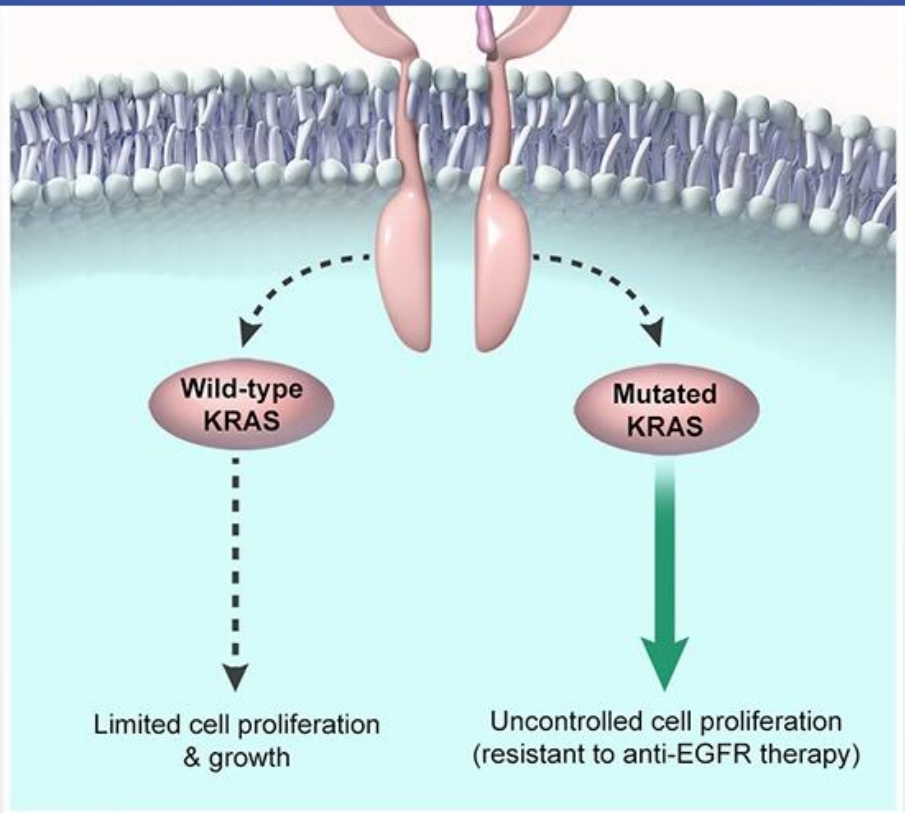

Epidermal growth factor receptor (EGFR) is stimulated in a paracrine or autocrine fashion by its ligands, leading to the **downstream activation of KRAS**, a membrane-bound GTP-binding protein that **stimulates cellular growth** and proliferation. Many cancers (eg, colorectal, pancreas) leverage this system to drive unchecked cellular growth by overexpressing EGFR and its ligands or by developing constitutive activating mutations

Settings

Item 4 of 40
Question Id: 12049

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

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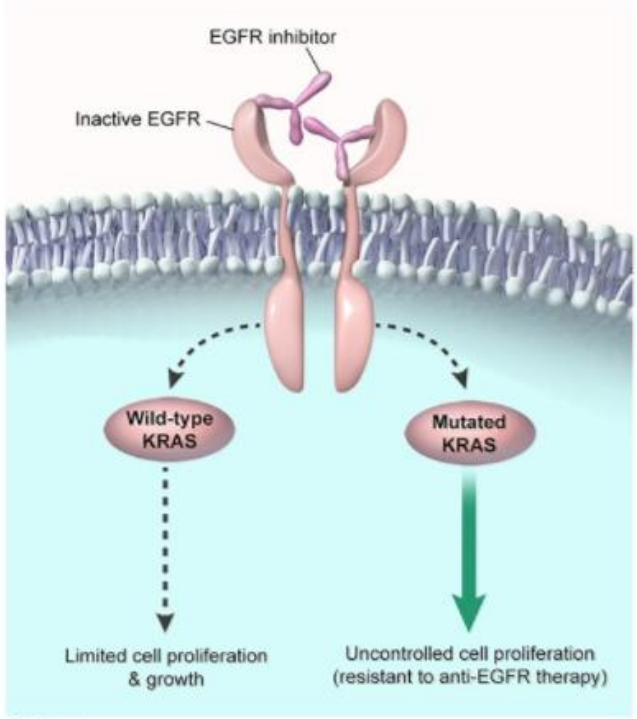
KRAS mutation causing anti-EGFR resistance



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leverage this system to drive unchecked cellular growth by overexpressing EGFR and its ligands or by developing constitutive activating mutations

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2/10/2019

Epidermal growth factor receptor (EGFR) is stimulated in a paracrine or autocrine fashion by its ligands, leading to the **downstream activation of KRAS**, a membrane-bound GTP-binding protein that **stimulates cellular growth** and proliferation. Many cancers (eg, colorectal, pancreas) leverage this system to drive unchecked cellular growth by overexpressing EGFR and its ligands or by developing constitutive activating mutations in the *KRAS* proto-oncogene.

The EGFR signaling system can be targeted for cancer treatment through the use of **monoclonal antibodies** (eg, cetuximab, panitumumab) that **block EGFR**, leading to reduced KRAS stimulation and **decreased cellular growth**. However, this treatment is only effective for tumors with wild-type (normal) KRAS. Tumors with ***KRAS*-activating mutations** are **resistant** to anti-EGFR agents as they have a constitutive activation of a downstream signal that is independent of EGFR stimulation or blockade. Prior to the use of anti-EGFR agents, genetic testing of tumor tissue is performed to see if KRAS is wild-type (eligible for treatment) or mutated (noneligible).

(Choice A) Adenomatous polyposis coli is a tumor suppressor protein that helps degrade beta-catenin, preventing uncontrolled cell growth. Inherited inactivating gene mutations are responsible for familial adenomatous polyposis.

(Choice C) p53 is a tumor suppressor protein involved in DNA repair, apoptosis, and cell cycle control; mutations or deletions are present in a large percentage of human tumors.

(Choice D) Platelet-derived growth factor stimulates formation of new blood vessels and proliferation of fibroblasts and smooth muscle cells by binding to a receptor tyrosine kinase; mutations resulting in overexpression encourage tumor growth by promoting uncontrolled angiogenesis.

(Choice E) Vascular endothelial growth factor (VEGF) is the dominant growth factor involved in angiogenesis and lymph vessel development. Overexpression of VEGF promotes tumor vascularization, facilitating the growth and metastasis of cancers.

Educational objective:
Activating mutations of the *KRAS* gene lead to constitutive activation of the epidermal growth factor receptor (EGFR) pathway, promoting increased cell proliferation and growth. Tumors harboring these mutations are resistant to treatment with anti-EGFR drugs (eg, cetuximab, panitumumab).

Settings

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Item 5 of 40
Question Id: 1404

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

A 41-year-old previously healthy woman comes to the office due to weakness and easy fatigability. She also has had several episodes of epistaxis and gum bleeding. Physical examination reveals mucosal pallor. Further evaluation demonstrates that the patient has a clonal proliferation of white blood cells containing an abnormal protein. In an experiment, the abnormal cells from the patient are purified and cultured in 2 different plates, one with a vitamin A derivative (plate 1) and the other with control (plate 2). After several days of incubation, cells in plate 1 are well differentiated compared to those in plate 2, and clonal proliferation is inhibited. This patient most likely has which of the following conditions?

A. Acute lymphocytic leukemia
B. Acute myeloid leukemia
C. Chronic lymphocytic leukemia
D. Chronic myeloid leukemia
E. High-grade non-Hodgkin lymphoma

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Settings

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Item 5 of 40
Question Id: 1404

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

A 41-year-old previously healthy woman comes to the office due to weakness and easy fatigability. She also has had several episodes of epistaxis and gum bleeding. Physical examination reveals mucosal pallor. Further evaluation demonstrates that the patient has a clonal proliferation of white blood cells containing an abnormal protein. In an experiment, the abnormal cells from the patient are purified and cultured in 2 different plates, one with a vitamin A derivative (plate 1) and the other with control (plate 2). After several days of incubation, cells in plate 1 are well differentiated compared to those in plate 2, and clonal proliferation is inhibited. This patient most likely has which of the following conditions?

A. Acute lymphocytic leukemia [4%]
✔ B. Acute myeloid leukemia [83%]
C. Chronic lymphocytic leukemia [3%]
D. Chronic myeloid leukemia [7%]
E. High-grade non-Hodgkin lymphoma [1%]

Omitted
Correct answer
B

83%
Answered correctly

3 Seconds
Time Spent

11/09/2018
Last Updated

Explanation

Acute promyelocytic leukemia (APL), type M3 of acute myelogenous leukemia in the French-American-British classification system, results from a **t(15;17) mutation** whereby the gene for retinoic acid receptor alpha (*RARα*) is transferred from chromosome 17 to chromosome 15, where it fuses with the promyelocytic leukemia (*PML*) gene. This leads to the formation of a new gene called ***PML/RARα***. Normally, *RARα* plays a role in

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Explanation

Acute promyelocytic leukemia (APL), type M3 of acute myelogenous leukemia in the French-American-British classification system, results from a **t(15;17) mutation** whereby the gene for retinoic acid receptor alpha (*RARα*) is transferred from chromosome 17 to chromosome 15, where it fuses with the promyelocytic leukemia (*PML*) gene. This leads to the formation of a new gene called ***PML/RARα***. Normally, *RARα* plays a role in the proper differentiation of myeloid precursors, as the receptor interacts with retinoic acid to affect transcription of genes required for maturation. However, the t(15;17) mutation in APML causes transcription repression and produces an **abnormal receptor** that is unable to signal for the differentiation of myeloid precursors at physiologic doses of retinoic acid.

Treatment with **all-trans-retinoic acid** (ATRA), a vitamin A derivative, overcomes this (partly by inducing PML/RARα proteolysis) and stimulates differentiation of myeloblasts into mature granulocytes. ATRA therapy induces remission in about 90% of patients with APL. APL is associated with disseminated intravascular coagulation.

(Choice A) Acute lymphocytic leukemia predominantly affects children. Blast cells positive for the CD10 antigen (CALLA) suggest a good prognosis.

(Choice C) Chronic lymphocytic leukemia is frequently seen in elderly patients. It presents with lymphadenopathy, hepatosplenomegaly, and anemia, and has an indolent course. Neoplastic cells resemble mature B lymphocytes.

(Choice D) In chronic myeloid leukemia (also commonly manifesting in elderly patients with fatigue, leukocytosis, and splenomegaly), myeloid precursors in different stages of differentiation proliferate. This disease is caused by a t(9;22) translocation that forms the *BCR-ABL* fusion gene, which codes for an abnormal tyrosine kinase.

(Choice E) Several high-grade non-Hodgkin lymphomas are associated with cytogenetic abnormalities. t(8;14), t(2;8), and t(8;22) are typical for Burkitt lymphoma; these translocations involve the c-*myc* oncogene. Burkitt lymphoma is associated with Epstein-Barr virus infection and classically has a "starry sky" histologic appearance.

Educational objective:

Acute promyelocytic leukemia is the M3 variant of acute myelogenous leukemia. It affects adult patients and may present with disseminated

the proper differentiation of myeloid precursors, as the receptor interacts with retinoic acid to affect transcription of genes required for maturation. However, the t(15;17) mutation in APML causes transcription repression and produces an **abnormal receptor** that is unable to signal for the differentiation of myeloid precursors at physiologic doses of retinoic acid.

Treatment with **all-trans-retinoic acid** (ATRA), a vitamin A derivative, overcomes this (partly by inducing PML/RARα proteolysis) and stimulates differentiation of myeloblasts into mature granulocytes. ATRA therapy induces remission in about 90% of patients with APL. APL is associated with disseminated intravascular coagulation.

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Educational objective:
Acute promyelocytic leukemia is the M3 variant of acute myelogenous leukemia. It affects adult patients and may present with disseminated intravascular coagulation. The cytogenetic abnormality t(15;17) leads to formation of the promyelocytic leukemia-retinoic acid receptor alpha (*PML/RARα*) fusion gene, which is unable to signal for proper cellular differentiation, unlike the normal retinoic acid receptor.

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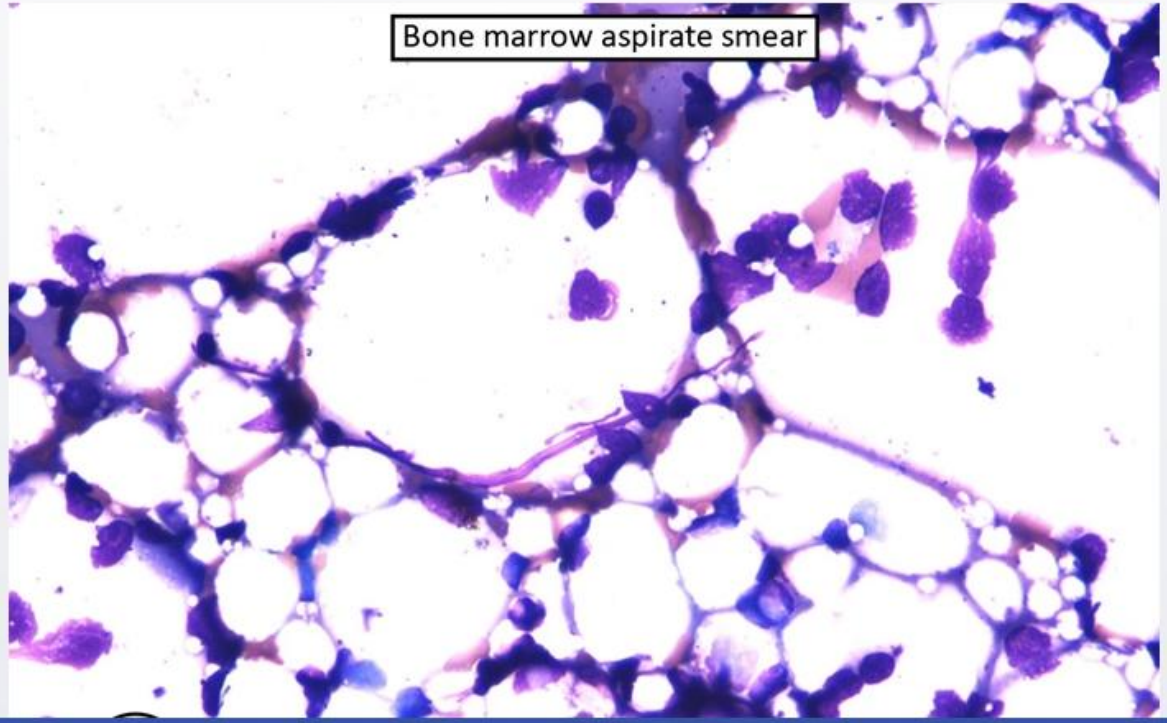
Item 6 of 40
Question Id: 1861

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

A 24-year-old man comes to the clinic due to progressive generalized weakness and fatigue over the last 2 weeks. He also has significant bruising on his trunk that developed spontaneously without any associated trauma. The patient has no known medical problems and takes no medications. His temperature is 37.1 C (98.8 F). Physical examination is notable for conjunctival pallor and truncal ecchymoses. Laboratory studies reveal a hemoglobin of 6.8 g/dL. Creatinine is normal. Bone marrow aspiration is performed. The aspirate is grossly pale and histologically appears dilute due to high lipid content.



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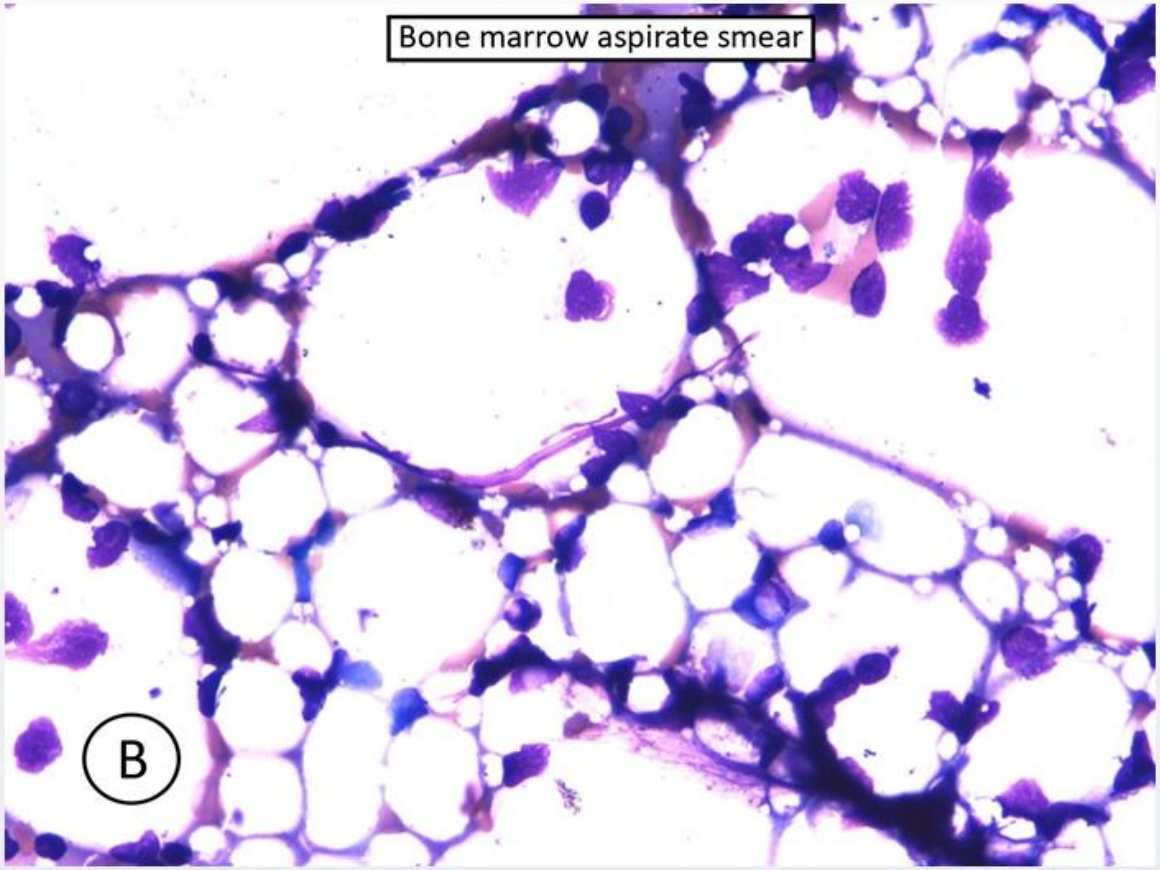
Item 6 of 40
Question Id: 1861

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



Which of the following blood parameters is most likely to be elevated in this patient?

Block Time Remaining: 00:00:33
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10 | Feedback | Suspend | End Block

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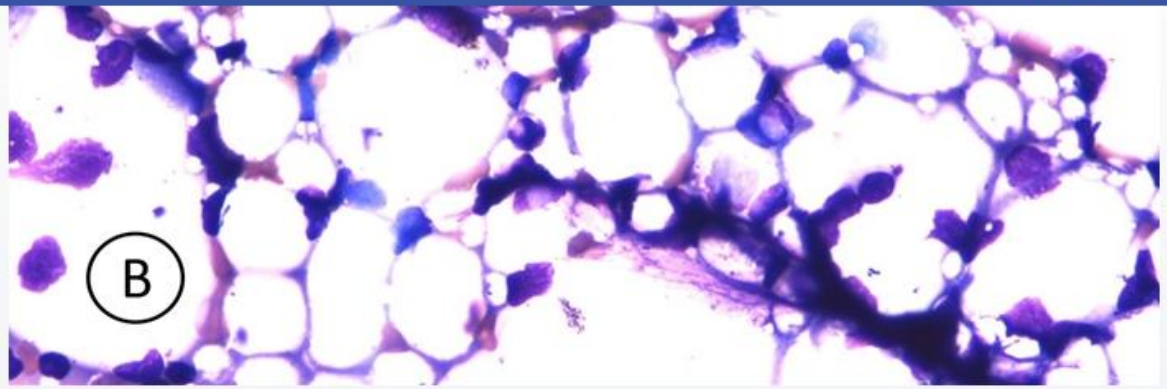
2/10/2019

Settings

Item 6 of 40
Question Id: 1861

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



Which of the following blood parameters is most likely to be elevated in this patient?

- A. Eosinophil count
- B. Erythropoietin
- C. Haptoglobin
- D. Iron
- E. Lactate dehydrogenase
- F. Reticulocyte index

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Block Time Remaining: 00:00:36
TUTOR

10 | Feedback | Suspend | End Block

4:08 PM
2/10/2019

Settings

Item 6 of 40
Question Id: 1861

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

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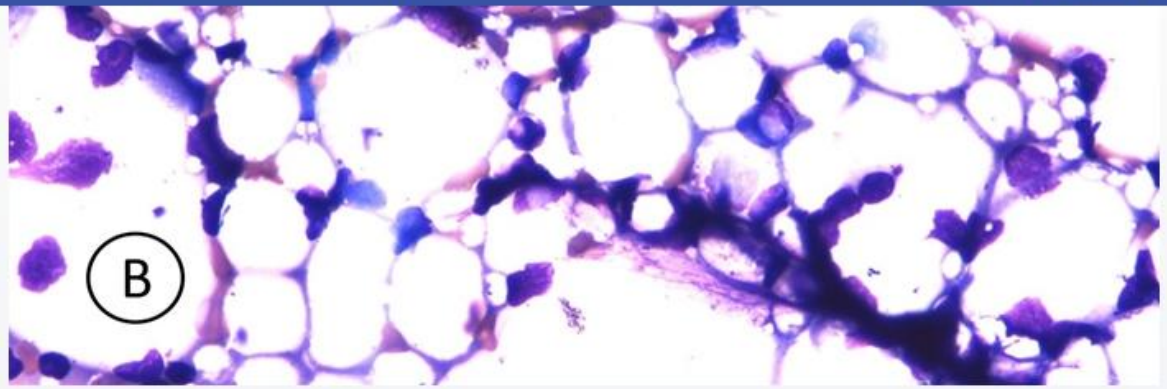

Which of the following blood parameters is most likely to be elevated in this patient?

- A. Eosinophil count [1%]
- ✔ B. Erythropoietin [75%]
- C. Haptoglobin [5%]
- D. Iron [1%]
- E. Lactate dehydrogenase [8%]
- F. Reticulocyte index [7%]

Omitted
Correct answer

75%
Answered correctly

10 Seconds
Time Spent

01/22/2019
Last Updated

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Explanation

This patient has:

- Fatigue, weakness, conjunctival pallor, and decreased hemoglobin, suggestive of anemia
- Bruising not associated with trauma, suggestive of thrombocytopenia
- High lipid content of the bone marrow aspirate, suggestive of hematopoietic cell aplasia or hypoplasia

He likely suffers from **aplastic anemia**, which is due to stem cell failure and actually affects all 3 cells lines, causing **pancytopenia** (despite the name).

As with most **anemias**, increased production of **erythropoietin** by the kidney (in response to anemia-induced hypoxia) would be expected, given this patient's normal renal function.

(Choice A) Aplastic anemia is associated with pancytopenia, which includes a reduction in circulating eosinophils.

(Choice C) Haptoglobin levels are typically normal in aplastic anemia. Haptoglobin is reduced in cases of intravascular hemolysis; once free hemoglobin binds haptoglobin, the resulting haptoglobin-hemoglobin complex is removed from circulation.

(Choice D) Serum iron is usually normal in aplastic anemia.

(Choice E) Elevated lactate dehydrogenase (LDH), particularly LDH-1, is expected in patients with hemolytic anemia, not aplastic anemia.

(Choice F) An increased reticulocyte index would be expected in a hemolytic or hemorrhagic anemia, assuming normal bone marrow function. Reticulocyte count is low in aplastic anemia because there are few progenitor cells in the marrow.

Educational objective:
The triad of low hemoglobin, thrombocytopenia, and absent hematopoietic cells in the bone marrow is consistent with aplastic anemia. A compensatory increase in circulating erythropoietin levels would be expected in individuals with aplastic anemia and normal renal function.

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Item 7 of 40
Question Id: 1873

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

A 34-year-old woman comes to the office due to vague abdominal pain over the past several months. She has no significant past medical history. The patient does not use tobacco or alcohol. Temperature is 36.7 C (98.1 F). On physical examination, right upper quadrant fullness is present. Abdominal imaging reveals a dense liver mass. Angiography shows a well-demarcated, highly vascularized tumor surrounded by normal liver parenchyma. Which of the following substances most likely contributed the most to blood vessel development in this patient's tumor?

A. Epidermal growth factor
B. Fibroblast growth factor
C. Insulin-like growth factor 1
D. Interferon-γ
E. Interleukin-1

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Item 7 of 40
Question Id: 1873

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

A 34-year-old woman comes to the office due to vague abdominal pain over the past several months. She has no significant past medical history. The patient does not use tobacco or alcohol. Temperature is 36.7 C (98.1 F). On physical examination, right upper quadrant fullness is present. Abdominal imaging reveals a dense liver mass. Angiography shows a well-demarcated, highly vascularized tumor surrounded by normal liver parenchyma. Which of the following substances most likely contributed the most to blood vessel development in this patient's tumor?

A. Epidermal growth factor [34%]
✔ B. Fibroblast growth factor [53%]
C. Insulin-like growth factor 1 [9%]
D. Interferon-γ [1%]
E. Interleukin-1 [1%]

Omitted
Correct answer
B

53%
Answered correctly

4 Seconds
Time Spent

10/30/2018
Last Updated

Explanation

This patient has a highly vascularized liver tumor, possibly a benign hepatic hemangioma. Many cases are discovered incidentally.
Angiogenesis (blood vessel formation) is predominantly driven by the following 2 substances:

- **Vascular endothelial growth factor** (VEGF): VEGF stimulates angiogenesis in a variety of tissues (normal, chronically inflamed, healing,

Block Time Remaining: 00:00:42
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Explanation

This patient has a highly vascularized liver tumor, possibly a benign hepatic hemangioma. Many cases are discovered incidentally.
Angiogenesis (blood vessel formation) is predominantly driven by the following 2 substances:

- **Vascular endothelial growth factor** (VEGF): VEGF stimulates angiogenesis in a variety of tissues (normal, chronically inflamed, healing, or neoplastic). As VEGF increases endothelial cell motility and proliferation, new capillaries begin to sprout.
- **Fibroblast growth factor** (FGF): FGF-2 is produced by a wide range of cells and is involved in endothelial cell proliferation, migration, and differentiation. FGF-2 also appears to play an important role in embryogenesis by stimulating angioblast production. As a group, FGFs not only contribute to angiogenesis, but also to embryonic development, hematopoiesis, and wound repair (by recruiting macrophages, fibroblasts, and endothelial cells to damaged tissues).

However, the laminin in basement membranes may pose a physical barrier to the sprouting of new blood vessels.

(Choice A) Epidermal growth factor (EGF), not to be confused with VEGF, has a mitogenic influence on epithelial cells, hepatocytes, and fibroblasts. EGF does not appear to play as important a role in angiogenesis as VEGF or FGF-2.

(Choice C) Insulin-like growth factor 1 (IGF-1), or somatomedin C, is synthesized predominantly by growth hormone-influenced hepatocytes and serves to stimulate cell growth and multiplication. IGF-1 does not appear to directly stimulate angiogenesis, but it can indirectly promote it by encouraging cell growth.

(Choices D and E) Although the proinflammatory nature of interleukin-1 (IL-1) can induce the release of other proinflammatory cytokines that trigger cellular VEGF expression, IL-1 does not appear to directly stimulate angiogenesis. Similarly, although interferon-γ can indirectly promote neovascularization through activation of macrophages (can release VEGF), it does not appear to directly stimulate angiogenesis.

Educational objective:
The key growth factors that promote angiogenesis in neoplastic and granulation tissue are vascular endothelial growth factor (VEGF) and fibroblast growth factor. Proinflammatory cytokines (eg, interleukin-1, interferon-γ) can indirectly promote angiogenesis through increased VEGF expression. The laminin in basement membranes may pose a physical barrier to the sprouting of new blood vessels.

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Item 8 of 40
Question Id: 1796

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

A 43-year-old Caucasian female complaining of reduced energy and fatigue is found to have hypochromic, microcytic anemia. Her past medical history is significant for stable angina treated with metoprolol and aspirin. Iron supplementation is prescribed. Several weeks later, a peripheral blood smear demonstrates numerous enlarged red blood cells that appear blue on Wright-Giemsa stain. The bluish color of these red blood cells is best explained by the presence of which of the following?

A. Hemoglobin precipitates
B. Nuclear membrane
C. Ribosomal RNA
D. Histones
E. Mitochondria
F. Golgi apparatus

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Block Time Remaining: 00:00:43
TUTOR

10 | Feedback | Suspend | End Block

4:09 PM
2/10/2019

Settings

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Item 8 of 40
Question Id: 1796

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

A 43-year-old Caucasian female complaining of reduced energy and fatigue is found to have hypochromic, microcytic anemia. Her past medical history is significant for stable angina treated with metoprolol and aspirin. Iron supplementation is prescribed. Several weeks later, a peripheral blood smear demonstrates numerous enlarged red blood cells that appear blue on Wright-Giemsa stain. The bluish color of these red blood cells is best explained by the presence of which of the following?

A. Hemoglobin precipitates [26%]
B. Nuclear membrane [12%]
✔ C. Ribosomal RNA [44%]
D. Histones [5%]
E. Mitochondria [10%]
F. Golgi apparatus [1%]

Omitted
Correct answer
C

44%
Answered correctly

3 Seconds
Time Spent

02/06/2019
Last Updated

Explanation

This patient suffers from hypochromic, microcytic anemia most likely caused by iron deficiency. Iron-deficient individuals on replacement therapy

Block Time Remaining: 00:00:45
TUTOR

10 | Feedback | Suspend | End Block

4:09 PM
2/10/2019

Omitted
Correct answer
C

44%
Answered correctly

3 Seconds
Time Spent

02/06/2019
Last Updated

Explanation

This patient suffers from hypochromic, microcytic anemia most likely caused by iron deficiency. Iron-deficient individuals on replacement therapy should experience hemoglobin level increases of approximately 2 g/dL per week for the first three weeks. This increase in hemoglobin results from enhanced erythropoiesis and the accelerated release of both mature red blood cells (RBCs) and reticulocytes into the bloodstream.

The reticulocyte is an immature RBC that is slightly larger and bluer than a mature RBC. It lacks a cell nucleus but retains a basophilic, reticular (mesh-like) network of residual ribosomal RNA. The ribosomal RNA appears blue microscopically after the application of the Wright-Giemsa stain.

After spending a day or so in the bloodstream, the reticulocytes are transformed into mature red blood cells that have a lifespan of approximately 120 days.

(Choices A, B, D, E, and F) The blue color of the reticulocyte is not caused by hemoglobin precipitates, nuclear membranes, histones, mitochondria, or the Golgi apparatus.

Educational Objective:
Increased bone marrow erythropoiesis results in an accelerated release of immature red blood cells (reticulocytes) into the bloodstream. Reticulocytes contain bluish cytoplasm and reticular precipitates of residual ribosomal RNA.

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28

Item 9 of 40
Question Id: 1717

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

Hypophosphorylated retinoblastoma protein is most likely to perform which of the following functions?

A. Induction of apoptosis
B. Prevention of the G1/S cell cycle transition
C. Activation of receptor tyrosine kinase
D. Opposition of p53 activity
E. Repair of damaged DNA

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Block Time Remaining: 00:00:48
TUTOR

10 | Feedback | Suspend | End Block

4:09 PM
2/10/2019

Settings

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Item 9 of 40
Question Id: 1717

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

Hypophosphorylated retinoblastoma protein is most likely to perform which of the following functions?

- A. Induction of apoptosis [6%]
- ✔ B. Prevention of the G1/S cell cycle transition [70%]
- C. Activation of receptor tyrosine kinase [6%]
- D. Opposition of p53 activity [13%]
- E. Repair of damaged DNA [3%]

Omitted
Correct answer
B

70%
Answered correctly

6 Seconds
Time Spent

02/06/2019
Last Updated

Explanation

The cell cycle is defined as the sequence of events that separates one cell division from the next. It consists of an inactive phase, interphase, and mitosis.

1. Gap phase 0 (G0 phase) is the stage in which the cell cycle is suspended. The cells are resting and do not divide.
2. Interphase comprises 90% of the cell cycle and is the stage in which the cell prepares for division. Interphase is subdivided into the G1 phase (ie, synthesis of RNA, protein, lipid, and carbohydrate), S phase (ie, DNA replication), and the G2 phase (ie, ATP synthesis).
3. Mitosis (M) is the stage in which the cell divides into two daughter cells

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3. Mitosis (M) is the stage in which the cell divides into two daughter cells.

At both the G1 to S phase transition and the G2 to M phase transition, the cell cycle can be stopped. These stages are called "checkpoints" and are regulated by cyclins and cyclin-dependent kinases that screen for DNA damage or abnormalities. Cells with normal DNA are allowed to proceed through the checkpoint, while cells with damaged DNA trigger DNA repair mechanisms. If the DNA damage is too substantial to be repaired, the cell undergoes apoptosis.

The Rb (retinoblastoma) tumor suppressor gene located on chromosome 13q14 encodes a nuclear phosphoprotein that regulates the G1→S checkpoint. Rb protein can be in an active (hypophosphorylated) state or an inactive (hyperphosphorylated) state. The inactivated Rb protein allows the cell to proceed through the G1→S checkpoint. The activated Rb protein, in contrast, stops the cell cycle. Abnormal phosphorylation of Rb protein results in its inactivation, thereby allowing cells with damaged DNA to proceed through the G1→S checkpoint and then divide. Mutations of the Rb protein have been linked to retinoblastoma, osteosarcoma, breast adenocarcinoma, small cell carcinoma of the lung, and bladder carcinoma.

(Choice A) The main inducer of apoptosis is the p53 protein, also described as the "molecular policeman."

(Choice C) The Rb protein does not activate receptor tyrosine kinase.

(Choice D) The Rb protein does not oppose p53 activity.

(Choice E) *BRCA1* and *BRCA2* are two of many DNA repair genes that have been identified. When mutated, these genes are associated with an increased risk of breast and ovarian cancer.

3. Mitosis (M) is the stage in which the cell divides into two daughter cells.

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(Choice D) The Rb protein does not oppose p53 activity.

(Choice E) *BRCA1* and *BRCA2* are two of many DNA repair genes that have been identified. When mutated, these genes are associated with an increased risk of breast and ovarian cancer.

Educational Objective:
The Rb tumor suppressor gene encodes the Rb protein, which regulates the cell cycle. Active (hypophosphorylated) Rb protein prevents damaged cells from proceeding past the G1 to S checkpoint, while the inactive (hyperphosphorylated) Rb protein allows the damaged cell to enter mitosis. Abnormal phosphorylation of Rb protein results in its inactivation.

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28

Item 10 of 40
Question Id: 1760

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

A 45-year-old woman comes to the office due to 2 weeks of persistent back pain. She has also had excessive fatigue, anorexia, and unintentional weight loss over the past several months. The patient has no prior medical problems but has a history of cancer in the family. An imaging study reveals a lytic lesion in the T10 vertebral body. Analysis of the biopsy sample shows cell lineage with abnormally high replicative potential. A genetic study reveals a single nucleotide substitution causing an activating mutation. Which of the following genes is most likely involved in this patient's disease?

A. *APC*
B. *BRCA1*
C. *KRAS*
D. *RB*
E. *TP53*

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10 | Feedback | Suspend | End Block

4:09 PM
2/10/2019

Settings

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Item 10 of 40
Question Id: 1760

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

A 45-year-old woman comes to the office due to 2 weeks of persistent back pain. She has also had excessive fatigue, anorexia, and unintentional weight loss over the past several months. The patient has no prior medical problems but has a history of cancer in the family. An imaging study reveals a lytic lesion in the T10 vertebral body. Analysis of the biopsy sample shows cell lineage with abnormally high replicative potential. A genetic study reveals a single nucleotide substitution causing an activating mutation. Which of the following genes is most likely involved in this patient's disease?

- A. *APC* [7%]
- B. *BRCA1* [18%]
- ✔ C. *KRAS* [45%]
- D. *RB* [13%]
- E. *TP53* [15%]

Omitted
Correct answer
C

45%
Answered correctly

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12/28/2018
Last Updated

Explanation

The role of oncogenes & tumor suppressors in cancer development

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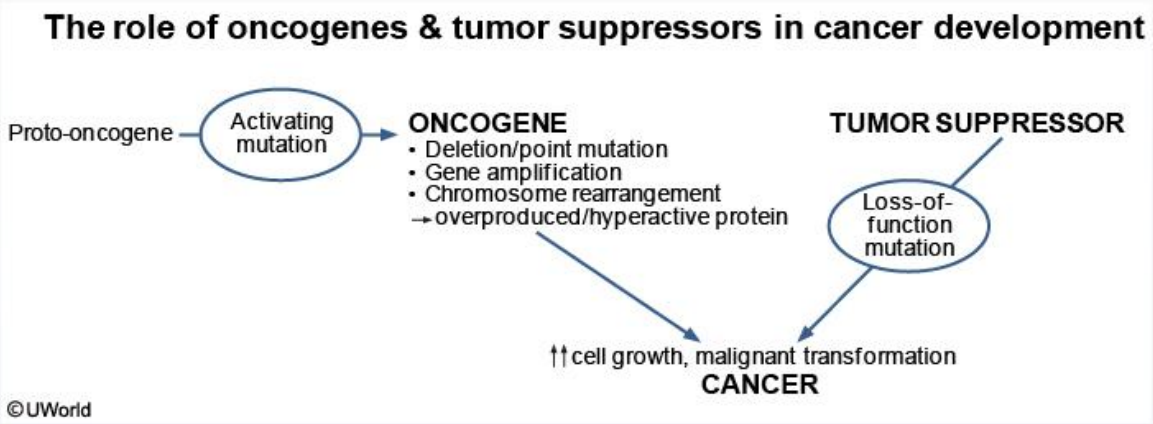
Explanation



Abnormal growth of neoplastic cells can arise due to mutation of either proto-oncogenes or anti-oncogenes (tumor suppressors). **Proto-oncogenes** stimulate cell proliferation, and their overexpression/amplification (eg, **activating** mutation) leads to increased cellular proliferation and neoplastic growth. ***KRAS*** is a proto-oncogene often activated in tumor cells, thereby increasing the cellular response to mitogenic stimuli.

In contrast, anti-oncogenes are **tumor suppressors** as they inhibit cellular proliferation. Their inactivation (eg, **loss-of-function** mutation) contributes to tumor development. *APC, BRCA1, RB*, and *TP53* are anti-oncogenes and are therefore more likely to be inactivated in neoplastic cells:

- *APC* is inactivated in familial adenomatous polyposis syndrome. Similar mutations are found in many sporadic colon cancers **(Choice A)**
- *BRCA1* is responsible for DNA repair. Its inactivation increases the risk of developing breast and ovarian cancer **(Choice B)**
- When active, *RB* suppresses the transition of cells from the G1 to S phase of the cell cycle, thereby inhibiting cellular proliferation. An inactivated *RB* is found in many tumors **(Choice D)**

Abnormal growth of neoplastic cells can arise due to mutation of either proto-oncogenes or anti-oncogenes (tumor suppressors). **Proto-oncogenes** stimulate cell proliferation, and their overexpression/amplification (eg, **activating** mutation) leads to increased cellular proliferation and neoplastic growth. ***KRAS*** is a proto-oncogene often activated in tumor cells, thereby increasing the cellular response to mitogenic stimuli.

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- *APC* is inactivated in familial adenomatous polyposis syndrome. Similar mutations are found in many sporadic colon cancers **(Choice A)**
- *BRCA1* is responsible for DNA repair. Its inactivation increases the risk of developing breast and ovarian cancer **(Choice B)**
- When active, *RB* suppresses the transition of cells from the G1 to S phase of the cell cycle, thereby inhibiting cellular proliferation. An inactivated *RB* is found in many tumors **(Choice D)**
- Mutated *TP53* is the most common abnormality associated with cancer development. *TP53* is a tumor suppressor gene that produces p53, a protein that inhibits proliferation of cells with genetic abnormalities **(Choice E)**

Some of the important proto-oncogenes, anti-oncogenes, and their associated tumors are listed in the **table**.

Educational objective:
Most tumors possess multiple cytogenetic abnormalities. Activation of proto-oncogenes results in stimulation of cellular proliferation. Inactivation of anti-oncogenes eliminates oversight of the cell cycle.

Exhibit Display

Proto-oncogenes/tumor promoters	Anti-oncogenes/tumor suppressors
• *ABL*: Chronic myeloid leukemia, acute lymphoblastic leukemia	• *APC*/β-catenin: Stomach cancer, colon cancer, pancreatic cancer, familial adenomatous polyposis
• *BRAF*: Melanoma	• *BRCA1, BRCA2*: Breast cancer, ovarian cancer
• *HER1*: Squamous cell lung cancer	• *DCC*: Colon cancer
• *HER2*: Breast cancer, ovarian cancer	• *NF1*: Neuroblastoma, neurofibromatosis type 1, sarcoma
• *MYC*: Neuroblastoma (*NMYC*); small cell lung cancer (*LMYC*)	• *RB*: Retinoblastoma, osteosarcoma, other cancers
• *RAS*: Lung cancer, colon cancer, pancreatic cancer (*KRAS*); renal cell cancer, bladder cancer (*HRAS*)	• *TP53*: Most cancers, Li-Fraumeni syndrome
• *SIS*: Astrocytoma, osteosarcoma	• *VHL*: Von Hippel-Lindau syndrome, renal cell cancer
• *TGFA*: Astrocytoma, hepatocellular carcinoma	• *WT1*: Wilms tumor

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A 35-year-old woman comes to the hospital due to sudden-onset numbness of the left arm and face. The patient has no weakness but has had several days of generalized headache, dyspnea on exertion, and easy fatigability. She has a history of well-controlled asthma. Temperature is 37.7 C (99.8 F), blood pressure is 110/60 mm Hg, and pulse is 80/min. Light touch sensation is decreased in the left upper extremity and the lower left face. Strength and reflexes are normal. Cardiopulmonary and abdominal examinations are unremarkable. She has no skin rash. Laboratory results are as follows:

Hemoglobin	8.6 g/dL
Platelets	24,000/mm^3
Blood urea nitrogen	32 mg/dL
Creatinine	1.9 mg/dL

Prothrombin time and activated partial thromboplastin time are normal. Peripheral blood smear shows numerous schistocytes. Urinalysis is positive for hematuria and proteinuria. Which of the following is the most likely primary pathogenesis of this patient's current condition?

A. IgA immune complex deposition
B. Impaired cleavage of von Willebrand factor
C. Plasma cell proliferation
D. Rupture of atheromatous plaque
E. Systemic coagulation factor activation

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Prothrombin time and activated partial thromboplastin time are normal. Peripheral blood smear shows numerous schistocytes. Urinalysis is positive for hematuria and proteinuria. Which of the following is the most likely primary pathogenesis of this patient's current condition?

A. IgA immune complex deposition [21%]
B. Impaired cleavage of von Willebrand factor [39%]
C. Plasma cell proliferation [7%]
D. Rupture of atheromatous plaque [9%]
E. Systemic coagulation factor activation [22%]

Explanation

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

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

This patient, who has new-onset neurologic symptoms, anemia with schistocytes, thrombocytopenia, and acute kidney injury, likely has **thrombotic thrombocytopenic purpura** (TTP). Her left arm and lower facial sensory loss are consistent with a pure sensory lacunar stroke, and her exertional dyspnea and easy fatigability are secondary to anemia. Patients may also develop cutaneous petechiae or purpuric lesions due to significantly low platelet counts.

TTP results from **deficiency of ADAMTS13**, a von Willebrand factor (vWF)-cleaving protease. Normally, circulating vWF (produced by megakaryocytes and endothelial cells) is released as large vWF multimers that are cleaved to their regular size by ADAMTS13. These vWF

This patient, who has new-onset neurologic symptoms, anemia with schistocytes, thrombocytopenia, and acute kidney injury, likely has **thrombotic thrombocytopenic purpura** (TTP). Her left arm and lower facial sensory loss are consistent with a pure sensory lacunar stroke, and her exertional dyspnea and easy fatigability are secondary to anemia. Patients may also develop cutaneous petechiae or purpuric lesions due to significantly low platelet counts.

TTP results from **deficiency of ADAMTS13**, a von Willebrand factor (vWF)-cleaving protease. Normally, circulating vWF (produced by megakaryocytes and endothelial cells) is released as large vWF multimers that are cleaved to their regular size by ADAMTS13. These vWF multimers aid hemostasis by bridging platelets and subendothelial components to sites of vascular injury. In TTP, the large **uncleaved vWF multimers** are significantly more prothrombotic and result in diffuse **microvascular thrombosis**. **Thrombocytopenia** and **microangiopathic hemolytic anemia** with schistocyte formation occur as erythrocytes are sheared by platelet-rich thrombi. Prothrombin time and partial thromboplastin time are usually normal as coagulation cascade activation plays a less significant role.

(Choice A) Henoch-Schönlein purpura (IgA vasculitis) is characterized by IgA immune complex deposition. Typical manifestations include palpable purpura, renal disease, and arthritis/arthralgias. Platelet counts are usually normal.

(Choice C) Some features of this presentation could be explained by plasma cell dyscrasias, such as multiple myeloma (renal failure, anemia due to bone marrow replacement, kidney injury) and Waldenström macroglobulinemia (neurologic symptoms due to hyperviscosity, autoimmune hemolytic anemia). However, microangiopathic hemolytic anemia would be unusual.

(Choice D) A cerebral vascular accident caused by plaque rupture could cause neurologic deficits but would not account for the concurrent hematologic and renal abnormalities.

(Choice E) Disseminated intravascular coagulation (eg, due to sepsis or major trauma) causes systemic activation of the coagulation cascade, leading to consumption of clotting factors and platelets. The classic presentation includes both thrombosis and bleeding as clotting factors are consumed rapidly, resulting in prolonged prothrombin and activated partial thromboplastin times.

Educational objective:
Thrombotic thrombocytopenic purpura results from impaired function of the von Willebrand factor (vWF)-cleaving protease ADAMTS13, resulting

thromboplastin time are usually normal as coagulation cascade activation plays a less significant role.

(Choice A) Henoch-Schönlein purpura (IgA vasculitis) is characterized by IgA immune complex deposition. Typical manifestations include palpable purpura, renal disease, and arthritis/arthralgias. Platelet counts are usually normal.

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Educational objective:
Thrombotic thrombocytopenic purpura results from impaired function of the von Willebrand factor (vWF)-cleaving protease ADAMTS13, resulting in uncleaved vWF multimers that are significantly more prothrombotic and cause diffuse microvascular thrombosis, microangiopathic hemolytic anemia, and thrombocytopenia.

References

- Thrombotic thrombocytopenic purpura: basic pathophysiology and therapeutic strategies.
- Pathophysiology of thrombotic thrombocytopenic purpura.
- Pathogenesis of thrombotic microangiopathies.

Settings

Item 11 of 40
Question Id: 11625

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

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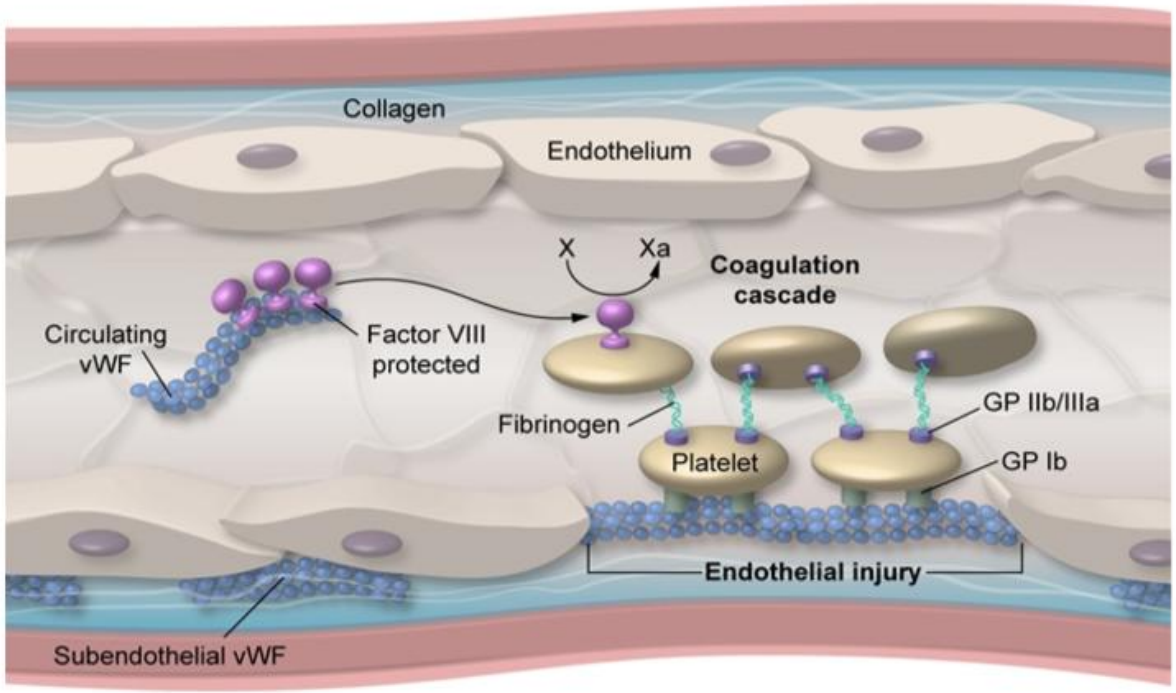
- Rituximab

Exhibit Display

Platelet adhesion & activation via vWF



GP = glycoprotein; vWF = von Willebrand factor.

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Item 12 of 40
Question Id: 1762

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A 47-year-old woman, gravida 2 para 2, comes to the office after noticing a pea-sized lump in her right breast while taking a shower. Her medical history is significant for 3 pack-years of cigarette use during her 20s. She underwent infertility treatment and in vitro fertilization for both of her pregnancies. The patient has no family history of breast or ovarian cancer. A clinical breast examination confirms the presence of a firm, fixed nodule in the right breast with a small patch of overlying puckered skin. Mammogram findings are highly suspicious for malignancy, and a needle biopsy reveals infiltrating ductal carcinoma. A right mastectomy and axillary lymph node dissection are scheduled. Overexpression of which of the following markers is most likely to be associated with aggressive disease in this patient?

A. BCL-2
B. Estrogen receptor
C. HER2
D. Mutated p53
E. Progesterone receptor

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Item 12 of 40
Question Id: 1762

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- A. BCL-2 [6%]
- B. Estrogen receptor [13%]
- ✔ C. HER2 [67%]
- D. Mutated p53 [11%]
- E. Progesterone receptor [1%]

Omitted
Correct answer
C

67%
Answered correctly

3 Seconds
Time Spent

10/12/2018
Last Updated

Explanation

Human epidermal growth factor receptor 2 (**HER2**, also called ERBB2) is a member of the epidermal growth factor receptor family. It is overexpressed in 20%-30% of **breast cancers**. HER2 is a transmembrane glycoprotein with **tyrosine kinase** activity that acts to increase cell

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C

Explanation

Human epidermal growth factor receptor 2 (**HER2**, also called ERBB2) is a member of the epidermal growth factor receptor family. It is overexpressed in 20%-30% of **breast cancers**. HER2 is a transmembrane glycoprotein with **tyrosine kinase** activity that acts to increase cell proliferation. It is present in diminutive amounts in normal breast and ovarian cells. In breast cancer, HER2 overexpression (positivity) is associated with **poorly differentiated, rapidly growing tumors**. Clinically, HER2 status is used to predict therapeutic response to anti-HER2 monoclonal antibodies (eg, trastuzumab).

(Choice A) Overexpression of the anti-apoptotic BCL-2 protein is classically observed in follicular lymphomas, but it also occurs in a variety of other malignancies, including breast cancer. Unlike in lymphomas, increased expression of BCL-2 in breast cancer is associated with a favorable prognosis.

(Choices B and E) Breast cancers that express high levels of estrogen and/or progesterone receptors are typically associated with improved outcomes. Activation of these receptors acts as a stimulus for tumor growth. Therefore, anti-estrogen therapy (eg, aromatase inhibitors, tamoxifen) is used to treat hormone receptor-positive breast cancer.

(Choice D) Overexpression of a mutated form of p53 is found in many human cancers, including breast cancers. However, the degree of protein expression does not correlate well with clinical outcomes. Rather, the effects on prognosis are more dependent on the specific mutation (eg, nonsense, gain of function).

Educational objective:
Estrogen- or progesterone-receptor positivity in breast cancer indicates expected sensitivity to tamoxifen and aromatase inhibitor treatment. HER2 overexpression in breast cancer suggests a more aggressive tumor that typically responds to therapy with the anti-HER2 monoclonal antibody trastuzumab.

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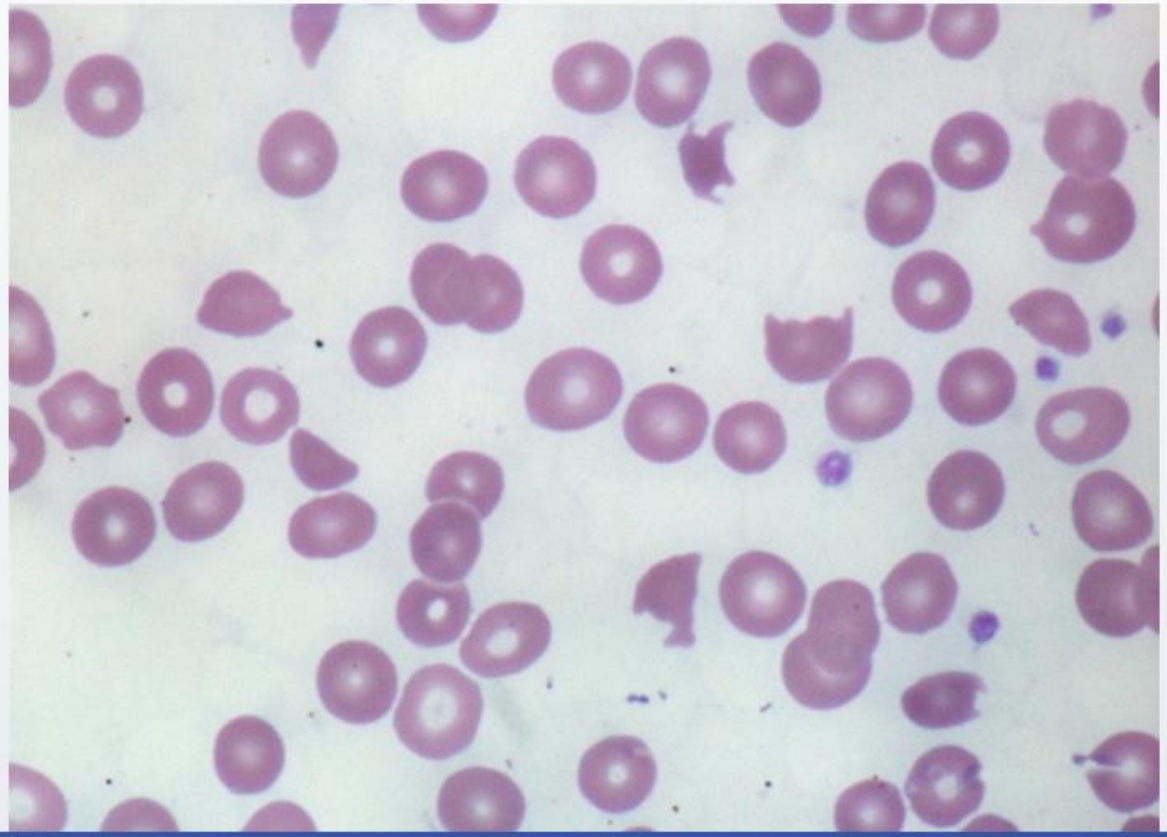
Item 13 of 40
Question Id: 829

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

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



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Item 13 of 40
Question Id: 829

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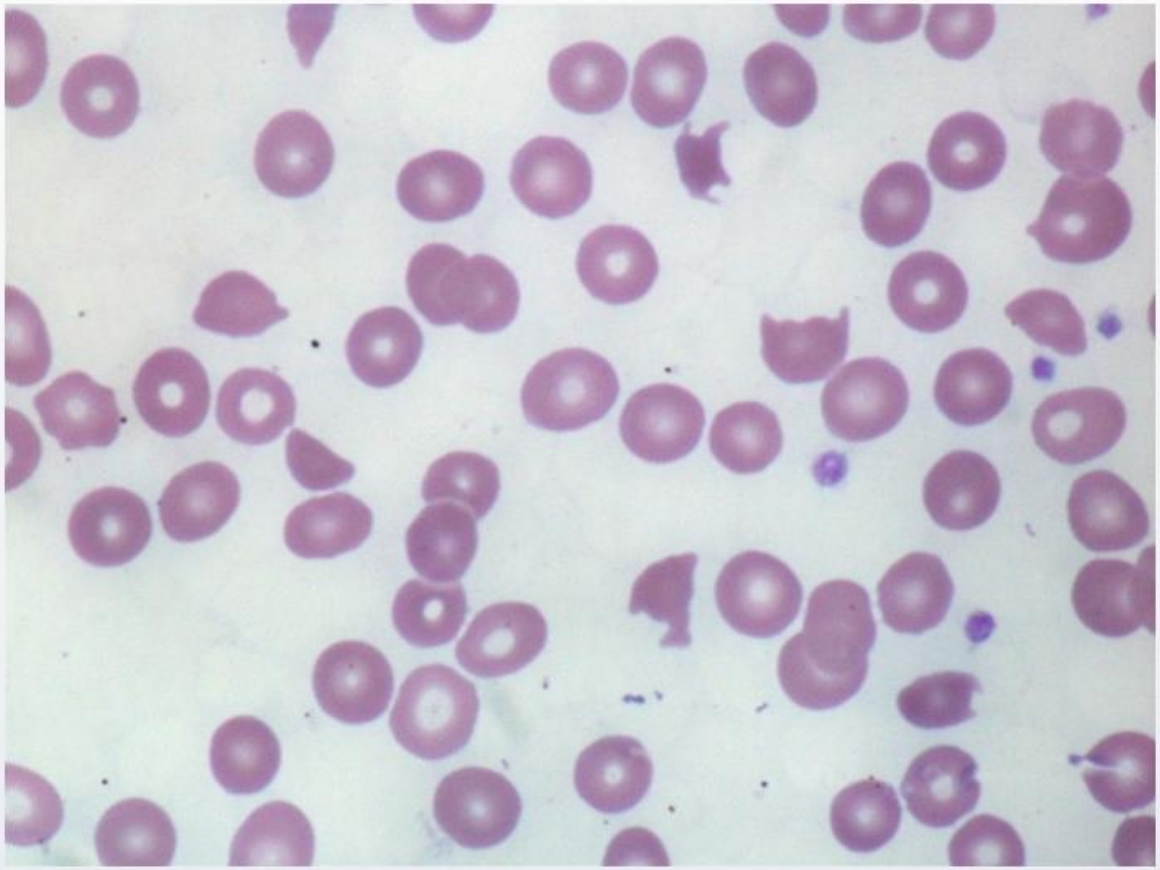

Which of the following laboratory findings is most likely to be seen in this patient?

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Item 13 of 40
Question Id: 829

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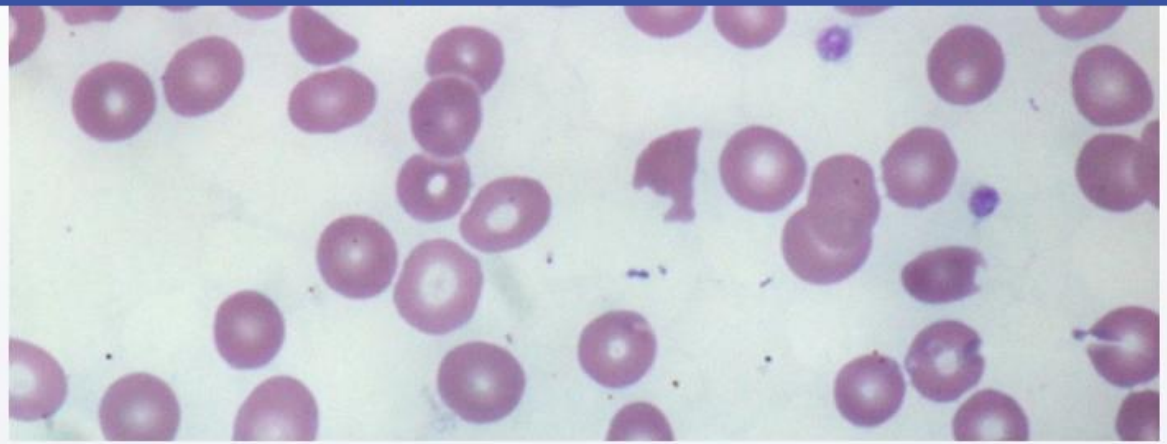

Which of the following laboratory findings is most likely to be seen in this patient?

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

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Item 13 of 40
Question Id: 829

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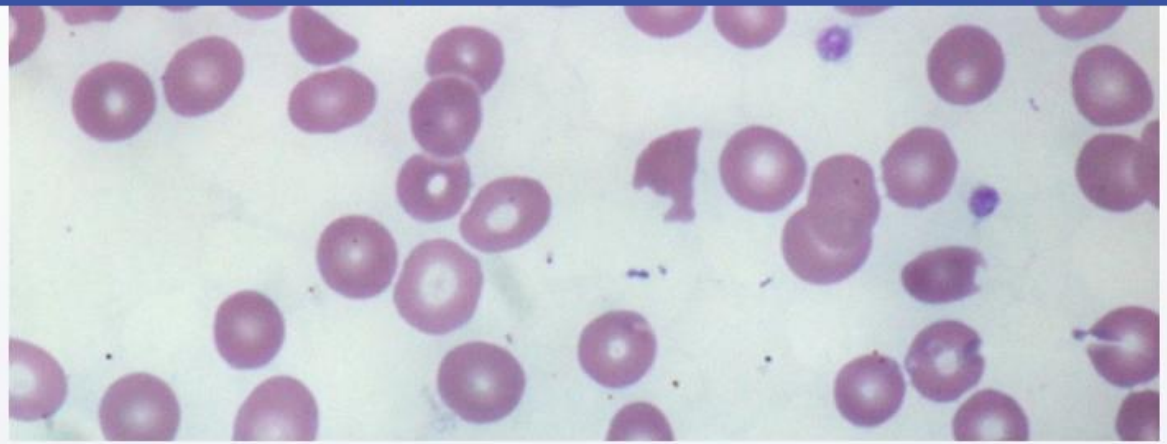

Which of the following laboratory findings is most likely to be seen in this patient?

- A. Increased total serum iron level [10%]
- ✔ B. Decreased serum haptoglobin level [76%]
- C. Increased mean corpuscular volume [6%]
- D. Decreased reticulocyte count [4%]
- E. Decreased serum albumin level [1%]

Omitted
Correct answer

76%
Answered correctly

9 Seconds
Time Spent

10/20/2018
Last Updated

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Item 13 of 40
Question Id: 829

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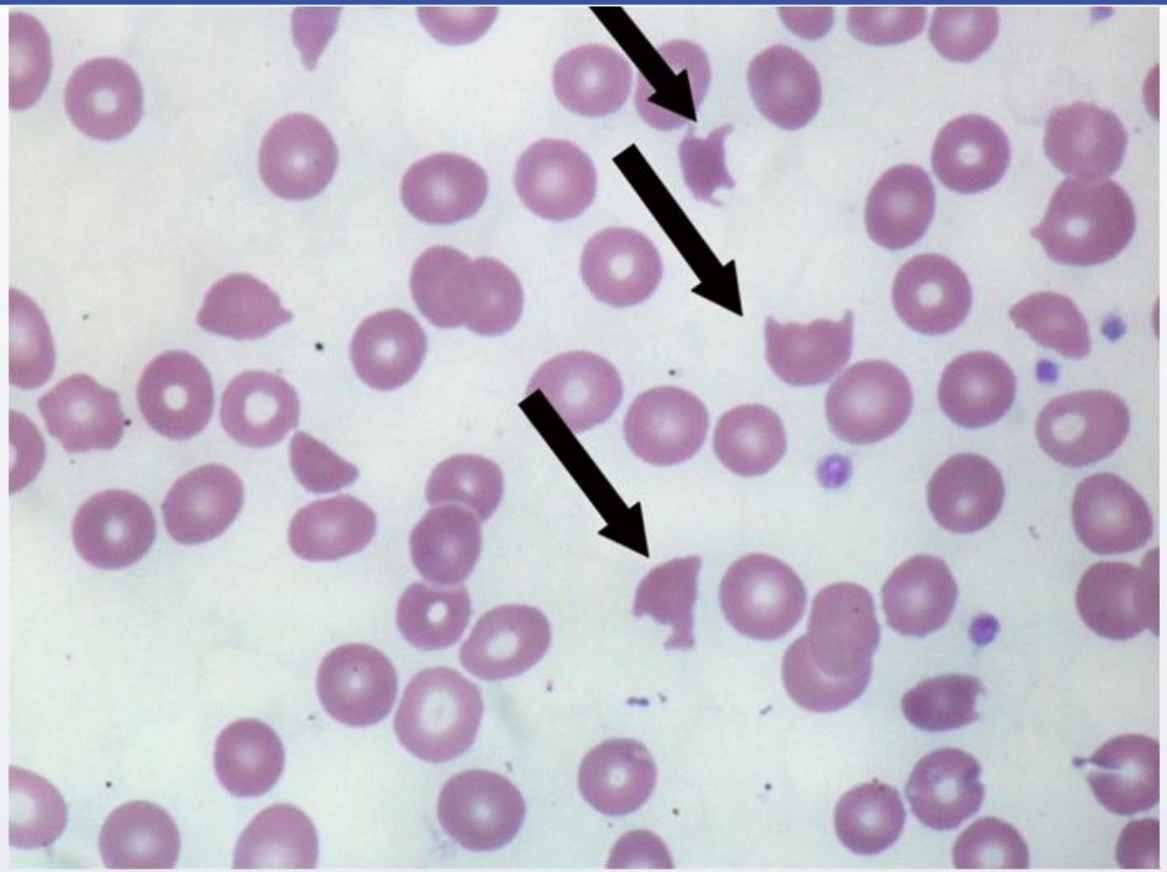

The fragmented erythrocytes shown on the slide above are called schistocytes or helmet cells. They are formed by mechanical trauma to erythrocytes as they circulate through the vasculature. This patient's schistocytes are most likely due to erythrocyte damage caused by his aortic

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The fragmented erythrocytes shown on the slide above are called schistocytes or helmet cells. They are formed by mechanical trauma to erythrocytes as they circulate through the vasculature. This patient's schistocytes are most likely due to erythrocyte damage caused by his aortic valve prosthesis. Artificial (mechanical) valves are more traumatic for RBCs than porcine prostheses and frequently cause hemolysis. Schistocytes can also be formed from narrowing of the vascular spaces due to fibrin strand formation, as seen in disseminated intravascular coagulation, hemolytic-uremic syndrome, and thrombotic thrombocytopenic purpura.

Hemolytic anemia due to intravascular erythrocyte destruction results in laboratory findings similar to those in other types of hemolytic anemias, including an increase in serum indirect bilirubin. Intravascular erythrocyte damage also results in free hemoglobin in serum (hemoglobinemia) and urine (hemoglobinuria) as well as increased serum lactate dehydrogenase (LDH). Haptoglobin is a serum protein that binds to free hemoglobin and promotes its uptake by the reticuloendothelial system. Haptoglobin levels decrease when significant quantities of hemoglobin are released into the circulation, as occurs with intravascular hemolysis.

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

(Choice C) Increased mean corpuscular volume (MCV) is a sign of megaloblastic anemia, which is most frequently caused by folate or Vitamin B12 deficiency. The peripheral blood smear in **megaloblastic anemia** shows hypersegmented neutrophils and enlarged ovoid erythrocytes. In contrast, schistocytosis may cause decreased MCV due to small RBC fragments being erroneously counted by automated hematology machines (this counteracts any increase in MCV due to reticulocytosis).

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

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

Educational objective:

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

Educational objective:
Schistocytes (helmet cells) are fragmented erythrocytes. They occur secondary to mechanical trauma from microangiopathic hemolytic anemias or prosthetic cardiac valves. Intravascular hemolytic anemias are characterized by decreased serum haptoglobin levels as well as increased LDH and bilirubin.

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Item 14 of 40
Question Id: 875

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

A 25-year-old woman comes to the physician with arthralgias in her hands for the last several months. The pain frequently involves her wrists and proximal finger joints bilaterally. It is sometimes worse in her wrists and at other times it is worse in her hands. The patient has no other medical problems and takes no medications. Her complete blood count is as follows:

Erythrocytes	3.2 million cells/μL
Platelets	90,000 /μL
Leukocytes	3,200 cells/μL

Further evaluation reveals proteinuria and red blood cell casts. Which of the following is the most likely diagnosis in this patient?

A. Ankylosing spondylitis
B. Myelodysplastic syndrome
C. Primary myelofibrosis
D. Systemic lupus erythematosus
E. Vitamin B_{12} deficiency

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Item 14 of 40
Question Id: 875

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

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Leukocytes	3,200 cells/μL

Further evaluation reveals proteinuria and red blood cell casts. Which of the following is the most likely diagnosis in this patient?

A. Ankylosing spondylitis [2%]
B. Myelodysplastic syndrome [13%]
C. Primary myelofibrosis [11%]
✔ D. Systemic lupus erythematosus [72%]
E. Vitamin B_{12} deficiency [0%]

Omitted
Correct answer
D

72%
Answered correctly

3 Seconds
Time Spent

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Last Updated

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2/10/2019

Manifestations of systemic lupus erythematosus	
Clinical symptoms	• **Constitutional**: fever, fatigue & weight loss • Symmetric, migratory **arthritis** • Skin: **butterfly rash** & **photosensitivity** • **Serositis**: pleurisy, pericarditis & peritonitis • Thromboembolic events (due to vasculitis & antiphospholipid antibodies) • Neurologic: cognitive dysfunction & seizures

Laboratory findings	• Hemolytic anemia, thrombocytopenia & leukopenia
	• **Hypocomplementemia** (C3 & C4)
	• Antibodies:
	  ◦ **ANA** (sensitive)
	  ◦ **Anti-dsDNA** & **anti-Smith** (specific)
	• Renal involvement: **proteinuria** & elevated creatinine

ANA = antinuclear antibodies; **dsDNA** = double-stranded DNA.

This patient displays a number of symptoms characteristic of systemic lupus erythematosus (SLE), a chronic autoimmune disorder affecting primarily women of childbearing age. Its prevalence is highest among African American women.

Hematologic abnormalities are common in patients with SLE and are frequently due to the formation of antibodies directed against blood cell autoantigens, resulting in a **type II hypersensitivity** response. Anemia in SLE is caused by autoimmune hemolysis, which develops due to formation of warm IgG antibodies against erythrocytes. It is characterized by spherocytosis, a positive direct Coombs test, and extravascular hemolysis. The pathogenesis of SLE-associated thrombocytopenia is identical to that of idiopathic thrombocytopenic purpura; antibodies against platelets are formed, causing their destruction. Leukopenia can also occur, due primarily to antibody-mediated destruction of neutrophils, but this

primarily women of childbearing age. Its prevalence is highest among African American women.

Hematologic abnormalities are common in patients with SLE and are frequently due to the formation of antibodies directed against blood cell autoantigens, resulting in a **type II hypersensitivity** response. Anemia in SLE is caused by autoimmune hemolysis, which develops due to formation of warm IgG antibodies against erythrocytes. It is characterized by spherocytosis, a positive direct Coombs test, and extravascular hemolysis. The pathogenesis of SLE-associated thrombocytopenia is identical to that of idiopathic thrombocytopenic purpura; antibodies against platelets are formed, causing their destruction. Leukopenia can also occur, due primarily to antibody-mediated destruction of neutrophils, but this is less common.

Immune complex deposition in the mesangium, subendothelial, and/or subepithelial spaces causes lupus nephritis via a **type III hypersensitivity** response. Histopathology is variable, depending on the site of immune deposition, but diffuse proliferative glomerulonephritis is the most common pattern. Urinalysis usually shows proteinuria and red blood cell casts.

(Choice A) Ankylosing spondylitis is a chronic inflammatory arthritis involving the spinal and sacroiliac joints causing low back pain. It is also associated with enthesitis, dactylitis, and uveitis. This patient's peripheral arthritis and renal findings make ankylosing spondylitis a less likely diagnosis than SLE.

(Choices B and C) Primary myelofibrosis and myelodysplastic syndrome are bone marrow disorders that occur most commonly in patients over 50 years of age. While they can cause pancytopenia, this patient has multisystem disease including arthritis and nephritis. Thus, SLE is a more likely diagnosis.

(Choice E) While vitamin B_{12} and folic acid deficiency can cause pancytopenia, this patient's history of concomitant arthritis and nephritis is more suggestive of SLE.

Educational objective:
Pancytopenia (decreased erythrocytes, leukocytes, and platelets) is common in patients with systemic lupus erythematosus. It frequently occurs due to the formation of autoantibodies against blood cells (type II hypersensitivity). In contrast, lupus nephritis is caused by immune complex deposition within the glomerulus (type III hypersensitivity).

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Item 15 of 40
Question Id: 1755

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

An 8-year-old boy comes to the office due to a mass in the right mandible. His family first noticed it a few months ago, and it has grown rapidly. He has had no fevers, chills, cough, or weight loss. The patient and his family recently immigrated to the United States from East Africa. He has no known medical problems. Temperature is 37 C (98.6 F). Physical examination shows a large tumor on the right mandible with palpable regional lymphadenopathy. A biopsy of the lesion is performed. Histopathologic examination shows a diffuse infiltrate of lymphoid cells with numerous mitotic figures. Interspersed macrophages surrounded by clear spaces are also seen. The gene translocated in these lymphoid cells produces a protein that is most directly responsible for which of the following functions?

A. Apoptosis inhibition
B. DNA repair
C. Regulation of G1 to S-phase transition
D. Transcription activation
E. Tyrosine kinase upregulation

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4:11 PM
2/10/2019

Settings

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Item 15 of 40
Question Id: 1755

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

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- A. Apoptosis inhibition [16%]
- B. DNA repair [2%]
- C. Regulation of G1 to S-phase transition [13%]
- ✔ D. Transcription activation [53%]
- E. Tyrosine kinase upregulation [14%]

Omitted
Correct answer
D

53%
Answered correctly

3 Seconds
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11/22/2018
Last Updated

Explanation

This patient likely has the endemic African form of **Burkitt lymphoma**, which primarily affects children and typically presents as a maxillary or mandibular mass. This type of lymphoma is strongly associated with **Epstein-Barr virus** (EBV) infection.

Block Time Remaining: 00:01:17
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2/10/2019

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28

Explanation

This patient likely has the endemic African form of **Burkitt lymphoma**, which primarily affects children and typically presents as a maxillary or mandibular mass. This type of lymphoma is strongly associated with **Epstein-Barr virus** (EBV) infection.

On light microscopy, **Burkitt lymphoma** consists of monomorphic, intermediate-sized lymphocytes with round nuclei, multiple prominent nucleoli, and vacuolated basophilic cytoplasm. A high mitotic index and high cell death rate are typically seen. Benign macrophages that phagocytize the resulting cellular debris (**"tingible body macrophages"**) are diffusely distributed throughout the malignant tissue. The clear spaces that surround these macrophages contribute to the characteristic **"starry sky" appearance** of Burkitt lymphoma.

Most Burkitt lymphomas demonstrate a translocation between the c-*Myc* oncogene on the long arm of chromosome 8 and the Ig heavy chain region on chromosome 14 [**t(8;14)**]. The product of c-*Myc* is a nuclear phosphoprotein that functions as a **transcription activator** controlling cell proliferation, differentiation, and apoptosis.

(Choice A) Follicular lymphoma is often characterized by a translocation between the long arm of chromosome 18 near the *BCL2* gene and the Ig heavy chain gene on chromosome 14 [t(14;18)]. This translocation leads to overexpression of the apoptosis inhibitor protein Bcl-2.

(Choice B) Mutations of DNA repair enzymes (eg, BRCA1, BRCA2) are associated with breast cancer, ovarian cancer, Lynch syndrome, xeroderma pigmentosum, Fanconi anemia, and many other diseases.

(Choice C) Translocation between the cyclin D1 locus on chromosome 11 and the Ig heavy chain locus on chromosome 14 [t(11;14)] is characteristic of mantle cell lymphoma. This abnormality results in increased production of cyclin D1, a promoter of G1 to S-phase transition during the cell cycle.

(Choice E) Translocation of the *ABL* gene from chromosome 9 to 22 [t(9;22)] results in the Philadelphia chromosome, a typical finding in chronic myelogenous leukemia. *BCR-ABL*, the resulting fusion gene, encodes a protein that inhibits apoptosis while promoting mitogenesis and increased tyrosine kinase activity.

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Educational objective:
Burkitt lymphoma is characterized by aggressive rapid growth and a "starry sky" microscopic appearance. Translocation of the c-*Myc* oncogene on the long arm of chromosome 8 with the Ig heavy chain region on chromosome 14 produces a nuclear phosphoprotein (c-Myc) that functions as a transcription activator.

Settings

Item 15 of 40
Question Id: 1755

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

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characteristic of mantle cell lymphoma. This abnormality results in increased production of cyclin D1, a promoter of G1 to S phase transition

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2/10/2019

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Item 15 of 40
Question Id: 1755

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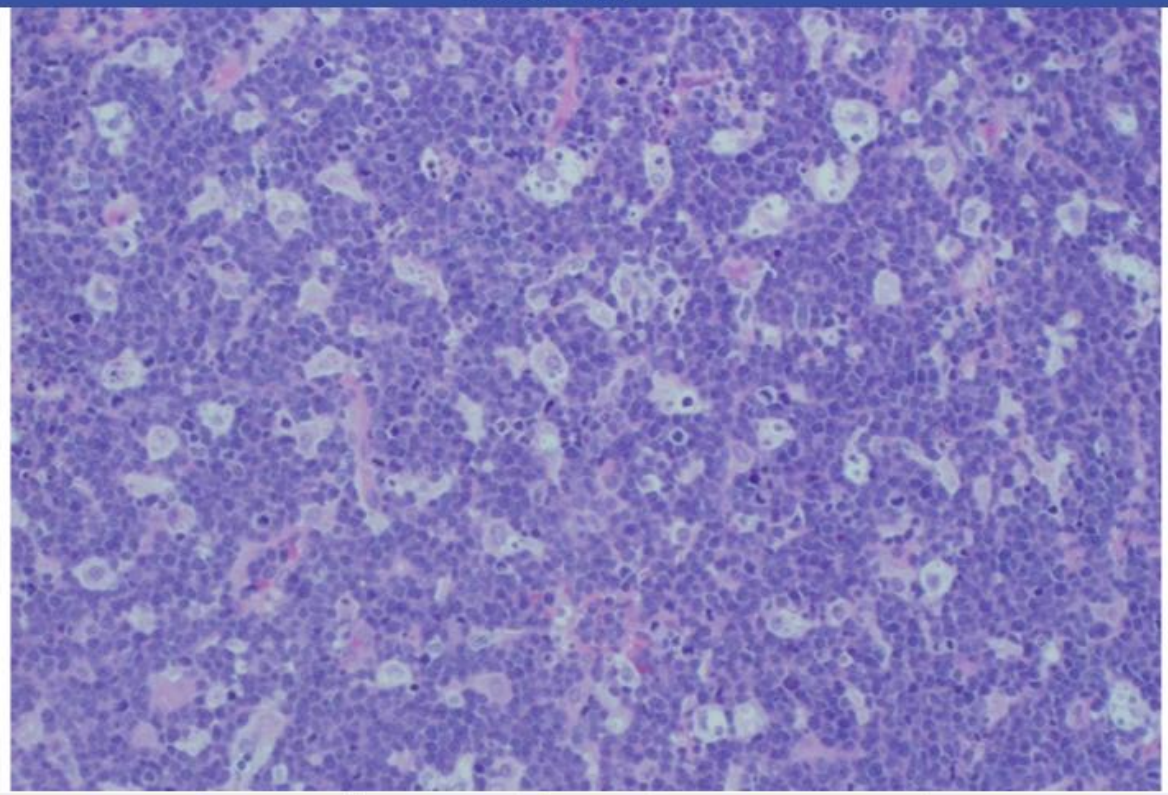

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characteristic of mantle cell lymphoma. This abnormality results in increased production of cyclin D1, a promoter of G1 to S phase transition

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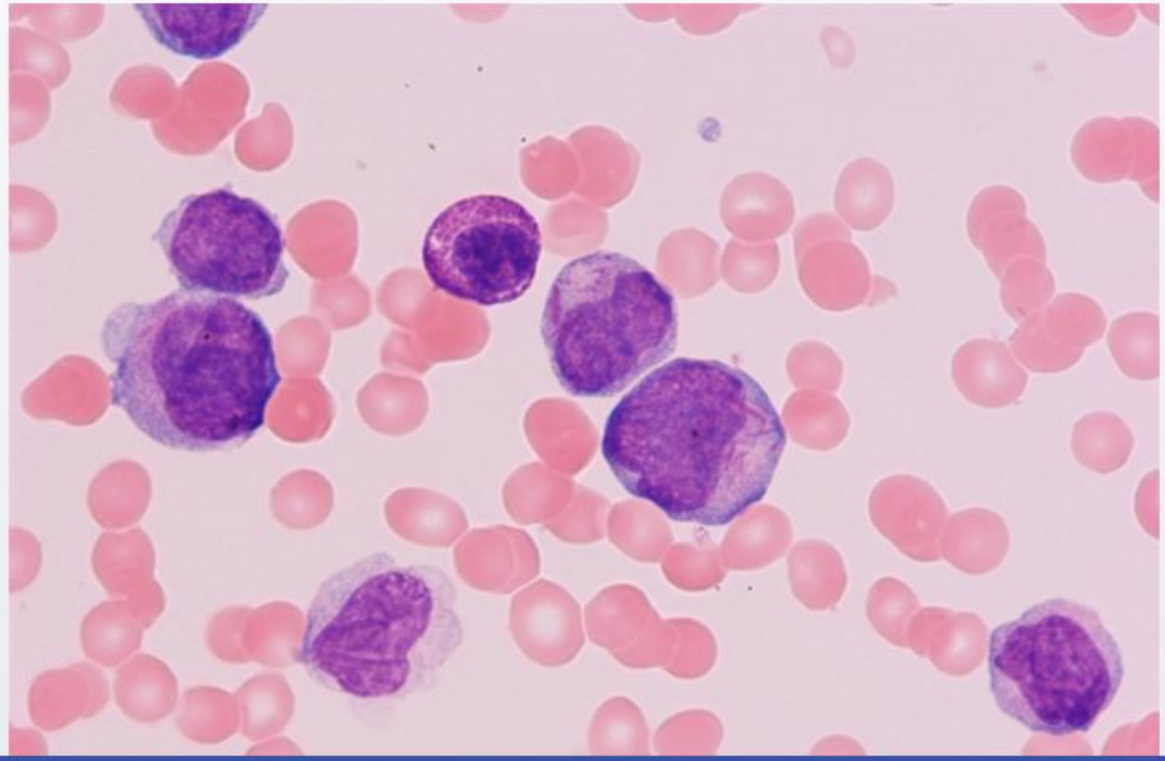
Item 16 of 40
Question Id: 1405

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

A 43-year-old man comes to the hospital due to recurrent episodes of fever and sore throat despite multiple courses of antibiotic therapy. For the past several months, he has also felt "run down" and fatigued all the time. His wife adds that he bruises easily and has had bleeding gums on several occasions. His temperature is 37.8 C (100.2 F). On examination, he has mucosal pallor, pharyngeal erythema, and multiple ecchymoses on his extremities. His peripheral blood smear is shown in the image below.



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Settings

Item 16 of 40
Question Id: 1405

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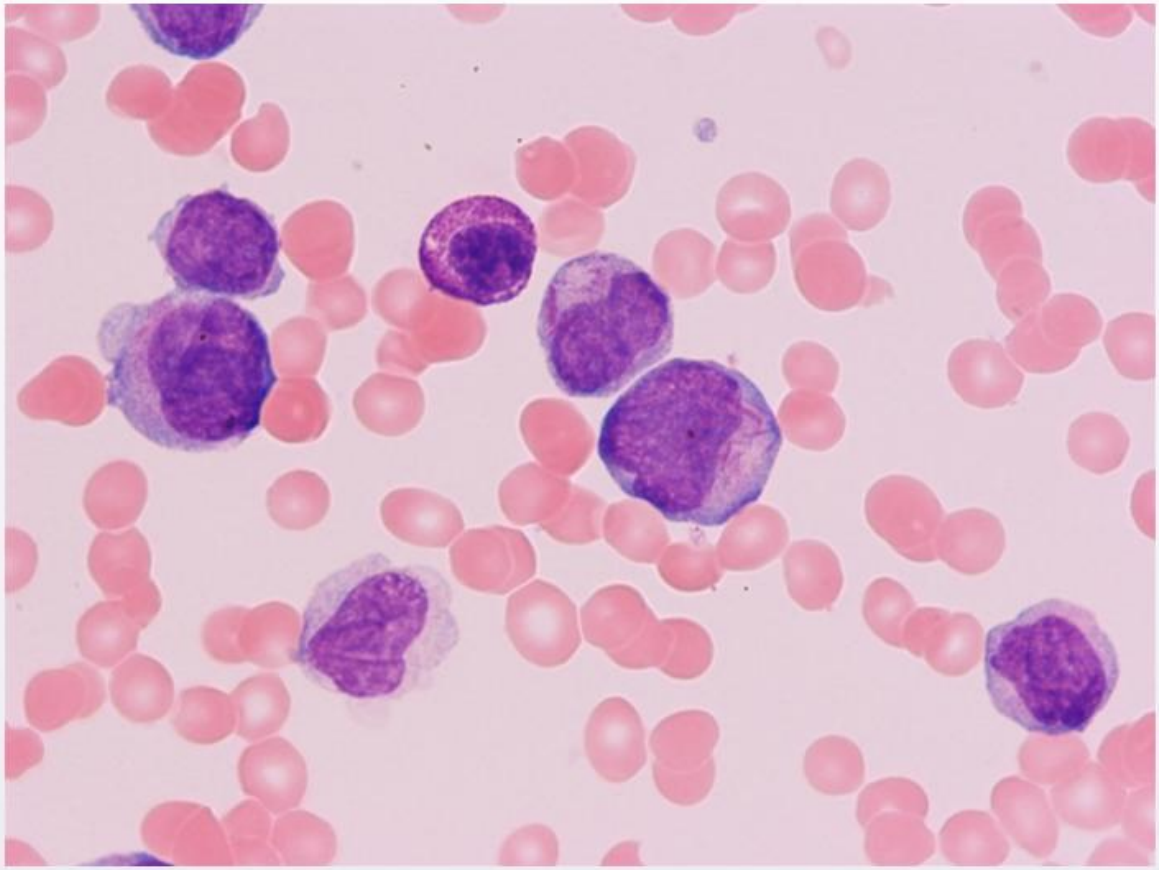

Which of the following chromosomal abnormalities is most likely present in the affected cells?

Block Time Remaining: 00:01:22
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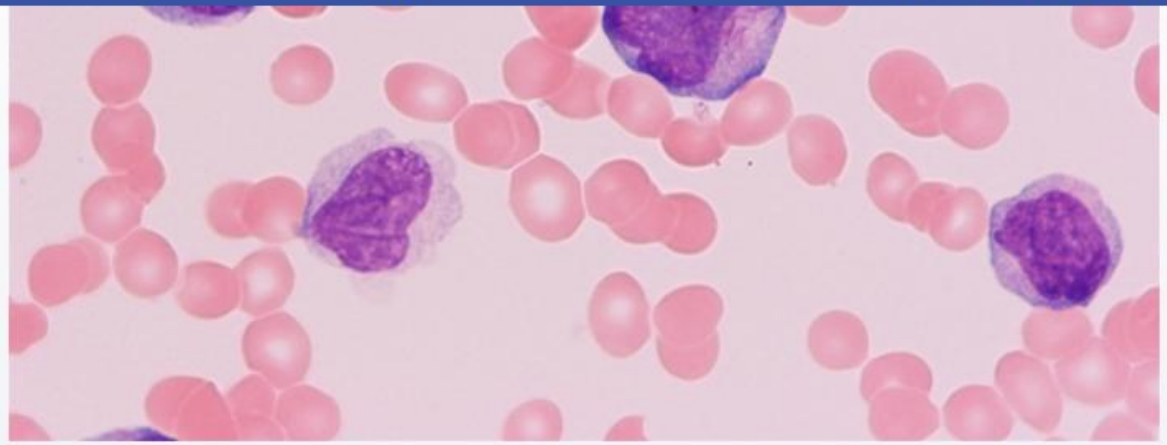
2/10/2019

Settings

Item 16 of 40
Question Id: 1405

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



Which of the following chromosomal abnormalities is most likely present in the affected cells?

- A. t(8;14)
- B. t(9;22)
- C. t(11;14)
- D. t(15;17)
- E. 13q-

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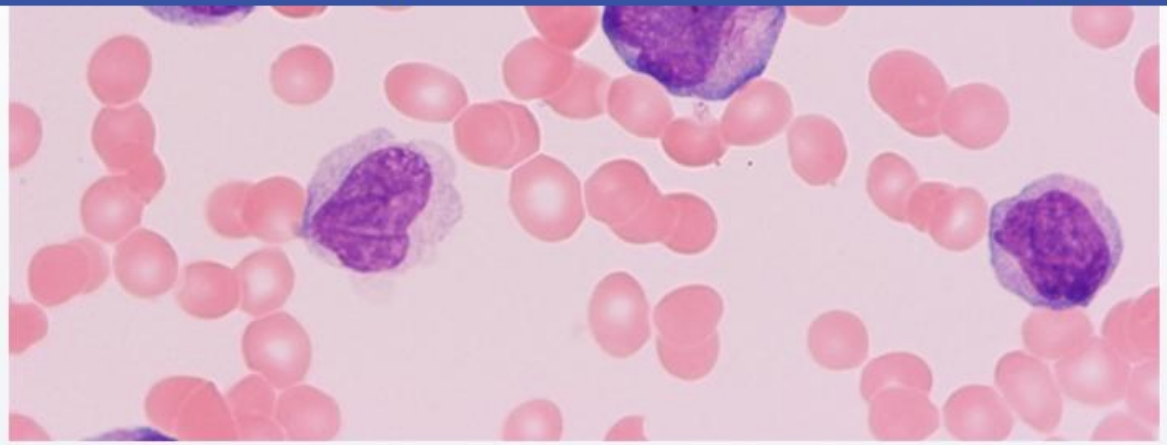
2/10/2019

Settings

Item 16 of 40
Question Id: 1405

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



Which of the following chromosomal abnormalities is most likely present in the affected cells?

- A. t(8;14) [6%]
- B. t(9;22) [21%]
- C. t(11;14) [5%]
- ✔ D. t(15;17) [66%]
- E. 13q- [0%]

Omitted
Correct answer

66%
Answered correctly

9 Seconds
Time Spent

12/06/2018
Last Updated

Block Time Remaining: 00:01:26
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Settings

Item 16 of 40
Question Id: 1405

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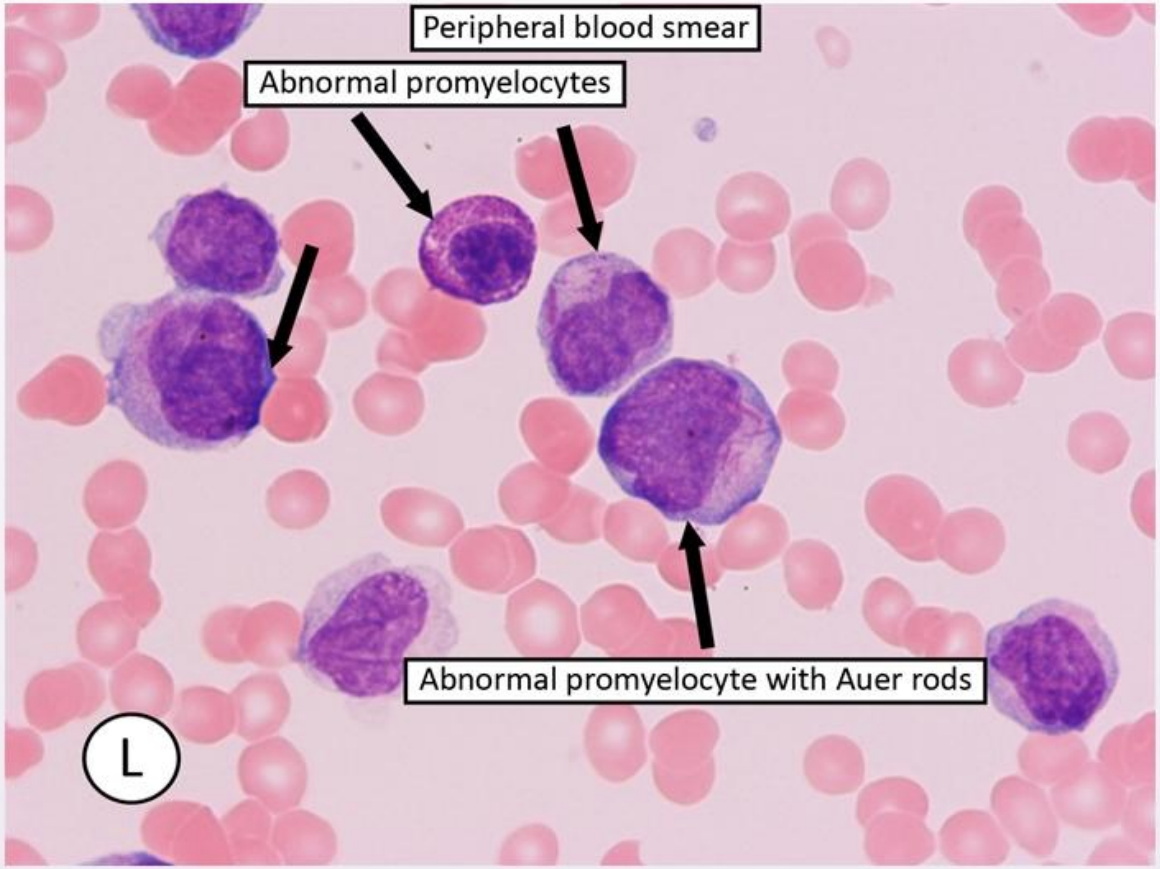

This patient has recurrent infections (possibly reflecting neutropenia), pallor (anemia), and ecchymoses (thrombocytopenia), with a peripheral blood smear that shows several abnormal myelocyte precursors containing coarse rod-shaped intracytoplasmic granules called **Auer rods**. This

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This patient has recurrent infections (possibly reflecting neutropenia), pallor (anemia), and ecchymoses (thrombocytopenia), with a peripheral blood smear that shows several abnormal myelocyte precursors containing coarse rod-shaped intracytoplasmic granules called **Auer rods**. This presentation is characteristic of **acute myelogenous leukemia** (AML). The **M3** variant of AML, **acute promyelocytic leukemia** (APML), characterized by the presence of promyelocytes on smear, is associated with disseminated intravascular coagulation (bleeding, thrombocytopenia, prolonged prothrombin and activated thromboplastin time). Affected cells exhibit the cytogenetic abnormality **t(15;17)**.

This cytogenetic change represents a translocation between the retinoic acid receptor alpha (*RARα*) gene on chromosome 17 and the promyelocytic leukemia (*PML*) gene on chromosome 15. Fusion of these 2 genes produces a chimeric gene product, *PML/RARα*, which codes for an abnormal retinoic acid receptor. This abnormal fusion gene inhibits promyelocyte differentiation and triggers the development of APML. Management is with all-trans retinoic acid.

(Choice A) With t(8;14), associated with Burkitt lymphoma, there is a translocation between the c-*Myc* protooncogene on chromosome 8 and the Ig heavy chain region on chromosome 14. This leads to increased production of the oncogene due to the frequency with which the Ig gene is transcribed.

(Choice B) Translocation of the *ABL* gene from chromosome 9 to chromosome 22 is characteristic of chronic myelogenous leukemia. t(9;22) forms the "Philadelphia chromosome" and results in the formation of a new gene, *BCR-ABL*, whose product has tyrosine kinase activity.

(Choice C) Mantle cell lymphoma is a B-cell malignancy associated with t(11;14). This translocation results in activation of the cyclin D gene.

(Choice E) Deletion of 13q is one of the molecular defects seen in chronic lymphocytic leukemia.

Educational objective:
The presence of rod-shaped intracytoplasmic inclusions known as Auer rods is characteristic of many forms of acute myeloblastic leukemia (AML). The M3 variant of AML, acute promyelocytic leukemia, is associated with the cytogenetic abnormality t(15;17).

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Item 17 of 40
Question Id: 789

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

A 70-year-old female presents to your office complaining of easy fatigability, exertional dyspnea and weight loss. She also complains of frequent falls. Physical examination reveals symmetrically decreased vibratory sensation to the lower extremities. Her hemoglobin is 7.8 g/dL and a peripheral blood smear shows hypersegmented neutrophils. Which of the following is the best treatment for this patient?

A. Iron preparations
B. Vitamin B12
C. Pyridoxine
D. Vitamin C
E. Folic acid
F. Erythropoietin
G. Filgrastim
H. Interleukin-2
I. Antithymocyte globulin

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4:12 PM
2/10/2019

Settings

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Item 17 of 40
Question Id: 789

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

A 70-year-old female presents to your office complaining of easy fatigability, exertional dyspnea and weight loss. She also complains of frequent falls. Physical examination reveals symmetrically decreased vibratory sensation to the lower extremities. Her hemoglobin is 7.8 g/dL and a peripheral blood smear shows hypersegmented neutrophils. Which of the following is the best treatment for this patient?

- A. Iron preparations [1%]
- ✔ B. Vitamin B12 [90%]
- C. Pyridoxine [1%]
- D. Vitamin C [0%]
- E. Folic acid [3%]
- F. Erythropoietin [1%]
- G. Filgrastim [0%]
- H. Interleukin-2 [0%]
- I. Antithymocyte globulin [0%]

Omitted
Correct answer
B

90%
Answered correctly

3 Seconds
Time Spent

02/06/2019
Last Updated

Block Time Remaining: 00:01:29
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2/10/2019

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Explanation

Deficiencies of folic acid and vitamin B12 are the most important causes of megaloblastic anemia. Both of these vitamins are required for DNA synthesis in erythropoiesis. When there is a deficiency of either of these vitamins, cell division is delayed, though the cytoplasm develops normally. Thus, the cells enlarge (megaloblasts) but do not divide. The bone marrow is hypercellular in megaloblastic anemia, but the megaloblastic erythroid precursor cells are rapidly destroyed in the bone marrow and few differentiated large RBCs are released into the circulation. In severe megaloblastic anemia, 90% of erythroid precursors are destroyed without ever entering the circulation.

Vitamin B12 and folic acid deficiencies cause similar hematological pictures. However, neurological dysfunction is only seen in patients with vitamin B12 deficiency. This is because B12 deficiency also causes axonal demyelination and degeneration. In late disease, the neurological dysfunction may be irreversible. The main sites of neurological involvement include the peripheral nerves, spinal cord (posterior and lateral columns), and the cerebrum. Decreased vibratory and position sense are early signs of vitamin B12 deficiency. Patients experience ataxia and recurrent falls because of compromised proprioception. Importantly, neurologic abnormalities can occur in vitamin B12 deficiency in the absence of frank anemia. Treating megaloblastic anemia due to vitamin B12 deficiency with folate alone could worsen the neurological dysfunction.

An RBC mean corpuscular volume (MCV) of more than 100 fL is suggestive of megaloblastic anemia. However, RBC macrocytosis can also occur in liver disease, hypothyroidism, and alcoholic liver disease. MCVs greater than 110 fL are typically seen only with vitamin B12 and folic acid anemias. On peripheral blood smear, there is macrocytosis (large RBCs), hypersegmented neutrophils, and large bizarrely shaped platelets. The presence of even a single neutrophil with more than 6 lobes should raise the suspicion of megaloblastic anemia.

The medications listed in the other answer choices are not used for the treatment of megaloblastic anemia.

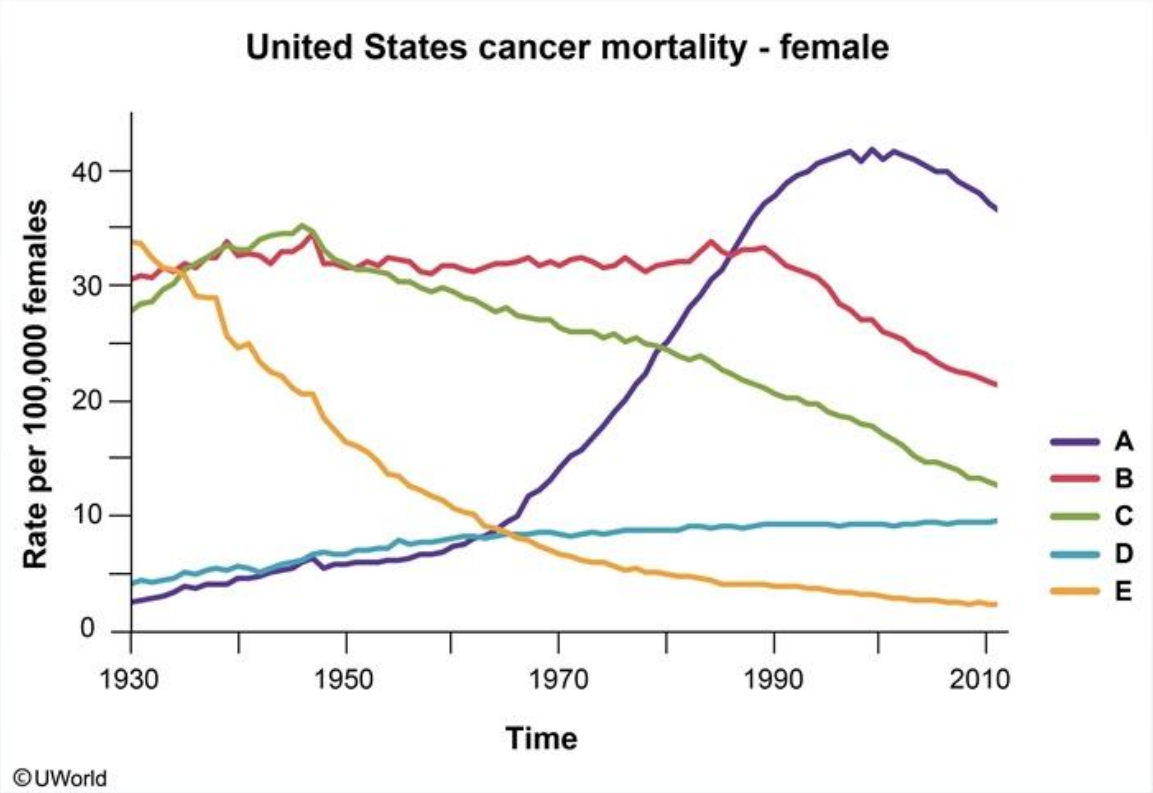
Educational Objective:
Vitamin B12 and folic acid deficiencies cause similar hematological pictures. However, neurological dysfunction is only seen in patients with vitamin B12 deficiency. If megaloblastic anemia due to vitamin B12 deficiency is mistakenly treated with folate alone, the neurologic dysfunction can worsen.

Settings

Item 18 of 40
Question Id: 1286

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

The age-adjusted mortality trends for 5 cancers in women in the United States are shown in the graph below.



Which of the following curves best corresponds to lung cancer?

Block Time Remaining: 00:01:31
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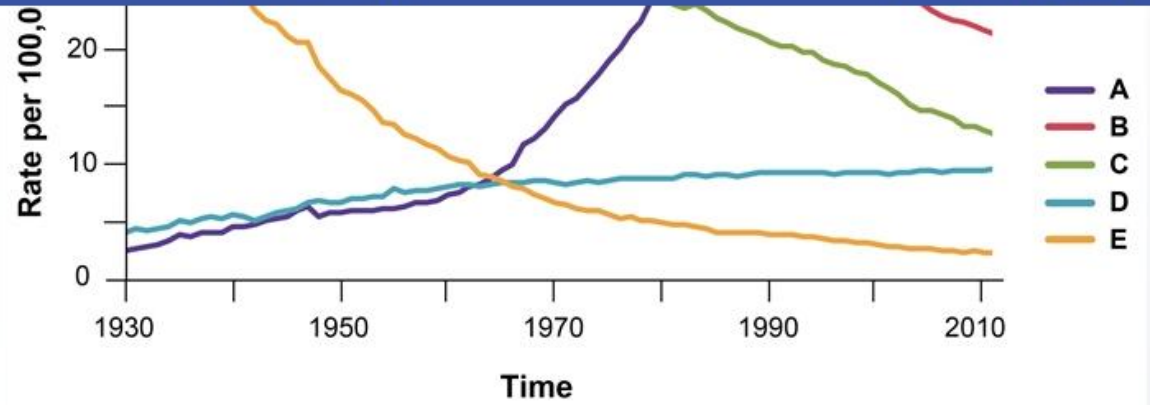
2/10/2019

Settings

Item 18 of 40
Question Id: 1286

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



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Which of the following curves best corresponds to lung cancer?

A. A
B. B
C. C
D. D
E. E

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Block Time Remaining: 00:01:34
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10 | Feedback | Suspend | End Block

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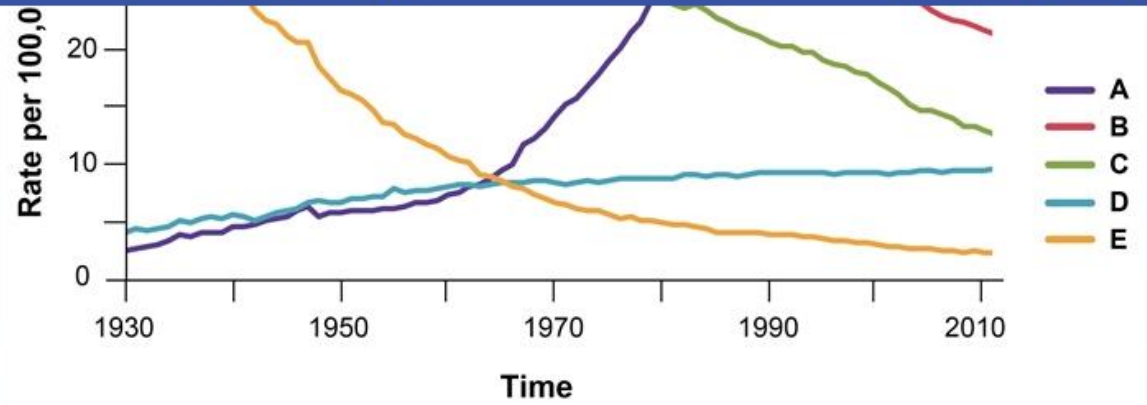
2/10/2019

Settings

Item 18 of 40
Question Id: 1286

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



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Which of the following curves best corresponds to lung cancer?

- A. A [78%]
- B. B [12%]
- C. C [3%]
- D. D [5%]
- E. E [0%]

Omitted
Correct answer

78%
Answered correctly

7 Seconds
Time Spent

12/26/2018
Last Updated

Block Time Remaining: 00:01:36
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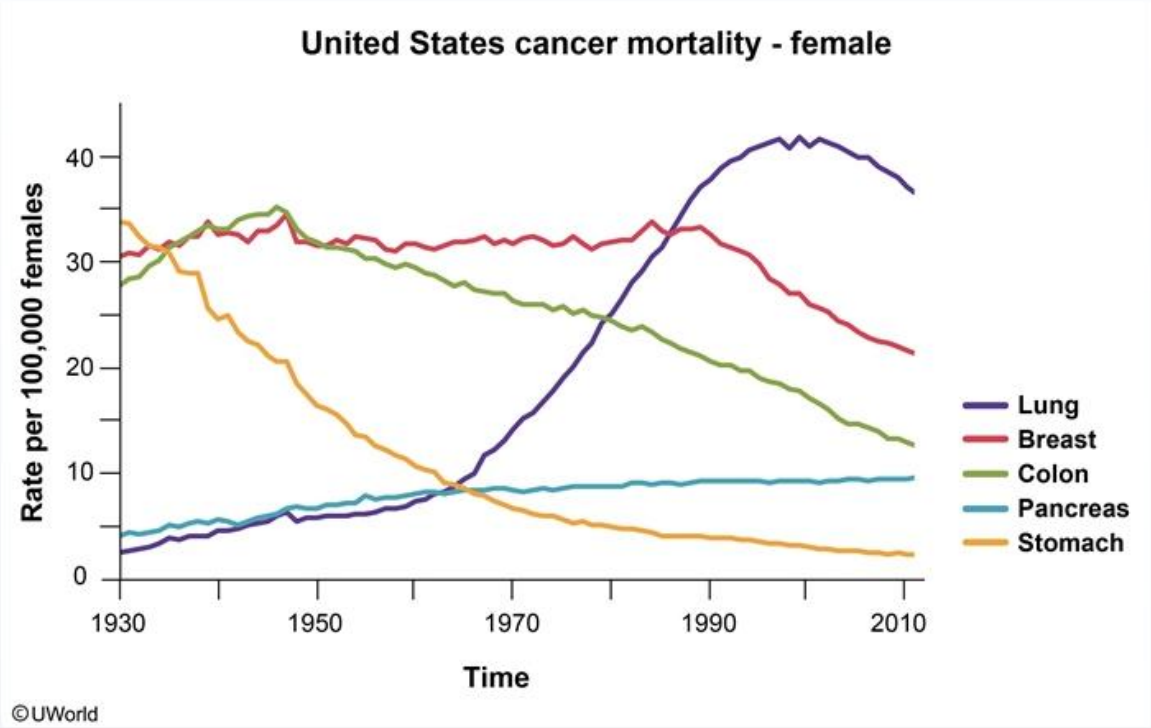
4:12 PM
2/10/2019

Settings

Item 18 of 40
Question Id: 1286

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

Explanation



Lung cancer has been the leading cause of **cancer mortality** in both **women** and men in the United States since the 1980s. **Tobacco use** (primary and secondhand) is the most important cause of lung cancer, particularly **non-small cell** lung cancer. Female use of cigarettes peaked in 1955, and mortality rates increased 20-50 years after smoking onset. Lung cancer mortality began to decrease after 2000, corresponding to a decline in tobacco use.

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Tobacco is a causative factor for numerous other cancers (eg, leukemia, nasopharyngeal, larynx, esophagus, pancreas, cervix, colon). It is directly carcinogenic to tissue by causing irritation and inflammation of the body's natural protective barriers. Patient education about tobacco's harmful effects is extremely important, as smoking cessation for even longtime users can be beneficial for reducing cancer risk and improving life expectancy.

(Choice B) Breast cancer is the most common non-skin cancer and the second most common cause of cancer death among women in the United States. Mortality from breast cancer began to decrease in the 1990s. Increased use of adjuvant chemotherapy and/or radiation and more frequent breast cancer screening are likely contributing factors to this decline.

(Choice C) Colon cancer mortality has decreased since the 1950s due to advances in surgical technique and adjuvant chemotherapy. Additional protective factors may include colorectal cancer screening, menopausal hormone therapy in women, and aspirin use.

(Choice D) The incidence and mortality of pancreatic cancer have increased in women over the last century and recently became the fourth most common cause of cancer death in women. Pancreatic cancer trends, like those of lung cancer, follow the pattern of increased smoking in women. However, lung cancer is responsible for three times more deaths than pancreatic cancer in women.

(Choice E) Stomach cancer incidence and mortality decreased drastically over the first half of the twentieth century. Proposed reasons include advances in refrigeration and food preservation (leading to decreased salt intake), and better sanitation and more adequate housing (reducing *Helicobacter pylori* infection rates).

Educational objective:
Between 1950 and 2000, rising rates of tobacco use resulted in an increase in female lung cancer incidence and mortality. Lung cancer is currently the most common cause of cancer death in both women and men in the United States.

Settings

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28

Item 18 of 40
Question Id: 1286

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

30

Exhibit Display

Cancer in United States populations: 2008-2012

	Highest incidence	Highest mortality
Female	1. Breast 2. Lung 3. Colon 4. Uterus 5. Thyroid	1. Lung 2. Breast 3. Colon 4. Pancreas 5. Ovary
Male	1. Prostate 2. Lung 3. Colon 4. Bladder 5. Melanoma	1. Lung 2. Prostate 3. Colon 4. Pancreas 5. Bladder

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Item 18 of 40
Question Id: 1286

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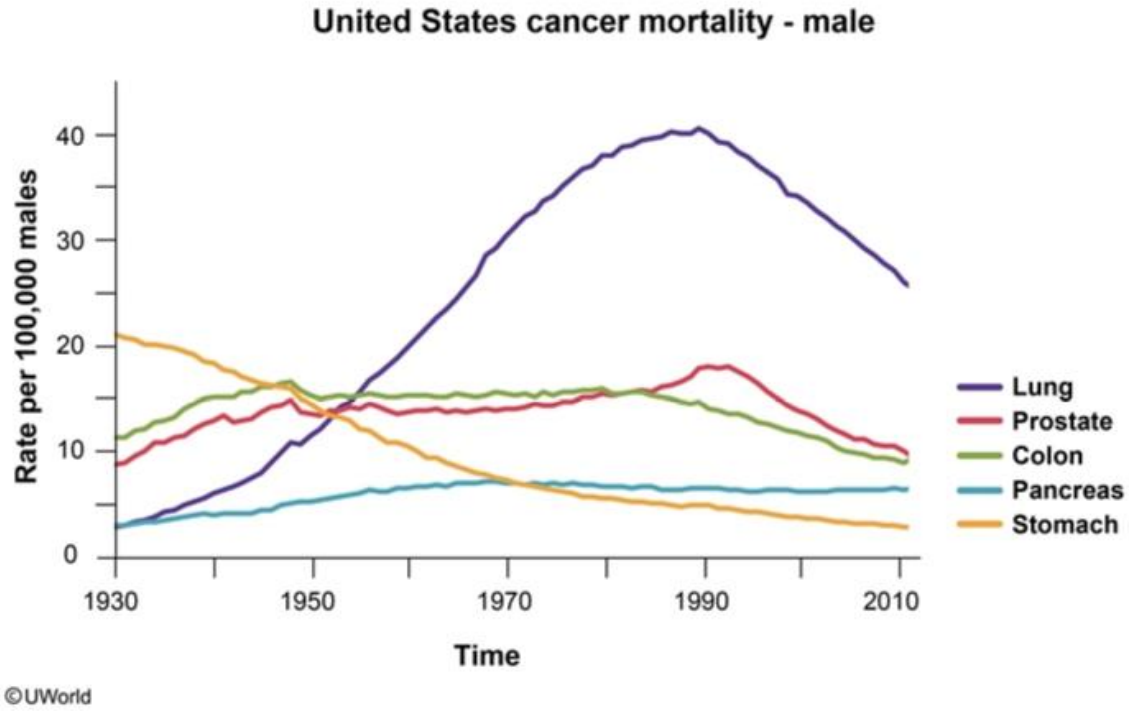
Exhibit Display



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Item 19 of 40
Question Id: 69

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

A 44-year-old woman comes to the office due to "indigestion." The patient often develops right upper quadrant abdominal discomfort and nausea after fatty meals, which subside spontaneously in several hours. She does not use tobacco, alcohol, or illicit drugs. The patient immigrated to the United States from Nepal 10 years ago. Abdominal ultrasound reveals numerous gallstones, and she undergoes elective laparoscopic cholecystectomy. The stones in her gallbladder have very low cholesterol content and appear small, dark, and spiculated. Which of the following conditions most likely predisposed this patient to gallstone formation?

A. Chronic hemolysis
B. Metabolic syndrome
C. Multiparity
D. Oral contraceptive use
E. Rapid weight loss

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2/10/2019

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1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28

Item 19 of 40
Question Id: 69

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A 44-year-old woman comes to the office due to "indigestion." The patient often develops right upper quadrant abdominal discomfort and nausea after fatty meals, which subside spontaneously in several hours. She does not use tobacco, alcohol, or illicit drugs. The patient immigrated to the United States from Nepal 10 years ago. Abdominal ultrasound reveals numerous gallstones, and she undergoes elective laparoscopic cholecystectomy. The stones in her gallbladder have very low cholesterol content and appear small, dark, and spiculated. Which of the following conditions most likely predisposed this patient to gallstone formation?

- A. Chronic hemolysis [85%]
- B. Metabolic syndrome [4%]
- C. Multiparity [3%]
- D. Oral contraceptive use [3%]
- E. Rapid weight loss [3%]

Omitted
Correct answer
A

85%
Answered correctly

3 Seconds
Time Spent

08/16/2018
Last Updated

Explanation

Pathogenesis of pigment stones

Block Time Remaining: 00:01:39
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Settings

Item 19 of 40
Question Id: 69

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

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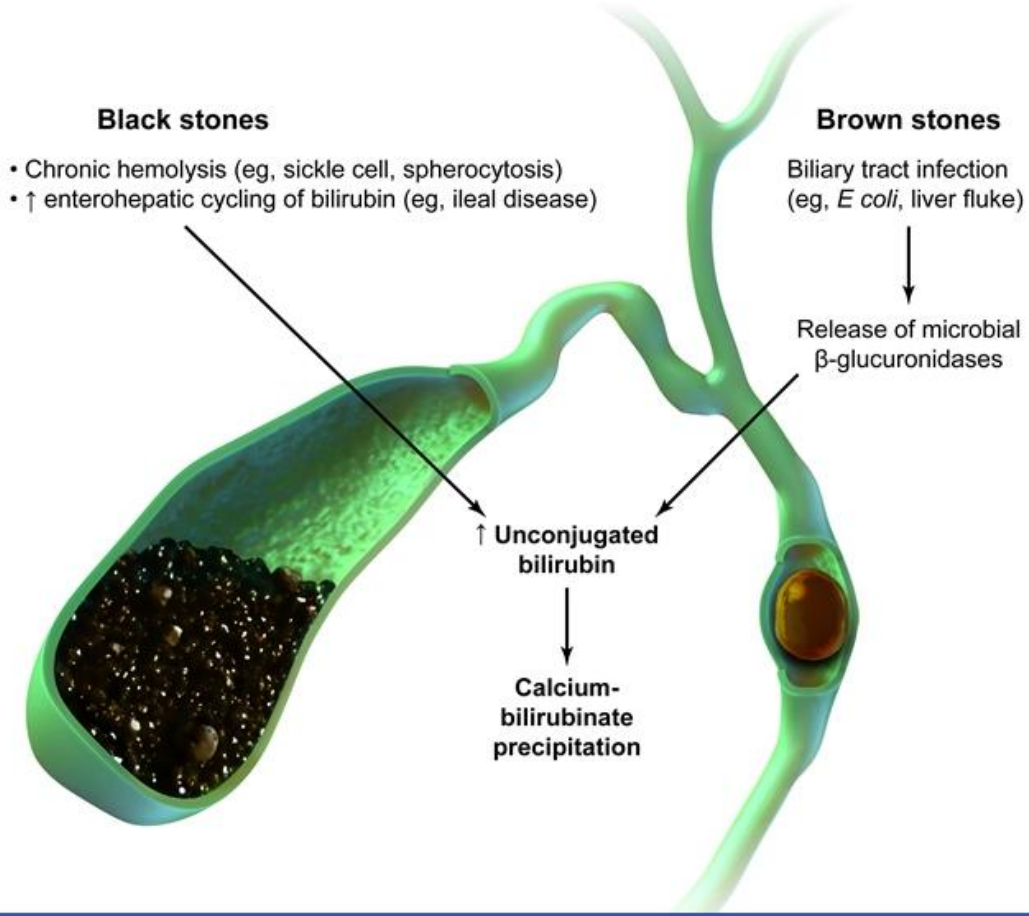
Pathogenesis of pigment stones



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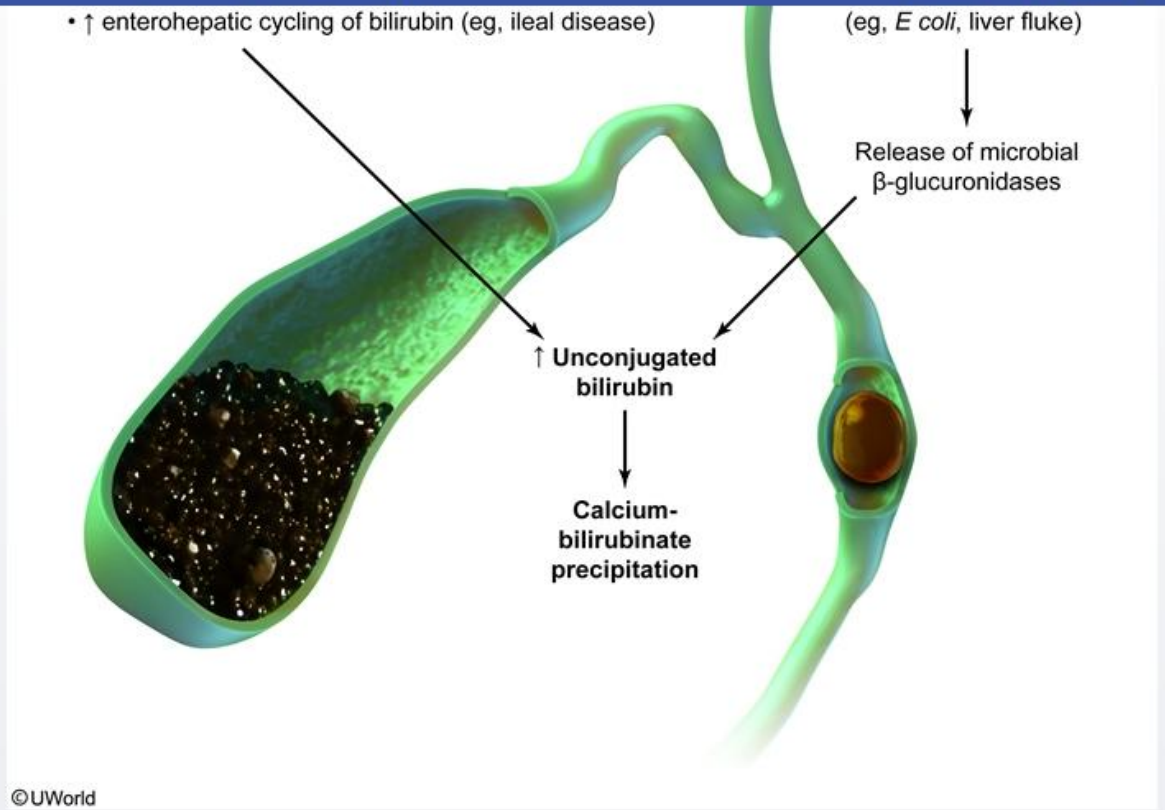

Gallstones are formed by the aggregation of bile constituents and are categorized as cholesterol stones, pigment stones, or mixed stones. **Pigment gallstones**, which account for only 10%-25% of gallstone cases in the United States, are most common in rural Asian populations. These stones can be brown to black and arise from conditions that increase the amount of **unconjugated bilirubin** in bile, which promotes calcium bilirubinate precipitation. Brown pigment stones are associated with biliary tract infections (microbes producing β-glucuronidases).

Gallstones are formed by the aggregation of bile constituents and are categorized as cholesterol stones, pigment stones, or mixed stones. **Pigment gallstones**, which account for only 10%-25% of gallstone cases in the United States, are most common in rural Asian populations. These stones can be brown to black and arise from conditions that increase the amount of **unconjugated bilirubin** in bile, which promotes calcium bilirubinate precipitation. Brown pigment stones are associated with biliary tract infections (microbes producing β-glucuronidases), whereas **black stones** occur in the setting of chronic **hemolysis** (eg, sickle cell anemia, β-thalassemia, hereditary spherocytosis) and increased enterohepatic cycling of bilirubin (eg, **ileal disease**).

Grossly, black pigment stones are usually present in significant numbers and are small, spiculated, and friable. Because these stones contain high amounts of calcium carbonates and phosphates, they are often radiopaque and appear on **x-ray**.

(Choices B, C, D, and E) Obesity/metabolic syndrome, multiparity, oral contraceptive use, and rapid weight loss are significant risk factors for development of cholesterol gallstones.

Educational objective:
Black pigment stones arise from conditions that increase the amount of unconjugated bilirubin in bile, which promotes calcium bilirubinate precipitation. This may occur in the setting of chronic hemolysis (eg, sickle cell anemia, β-thalassemia, hereditary spherocytosis) and increased enterohepatic cycling of bilirubin (eg, ileal disease).

References

- New pathophysiological concepts underlying pathogenesis of pigment gallstones.

Settings

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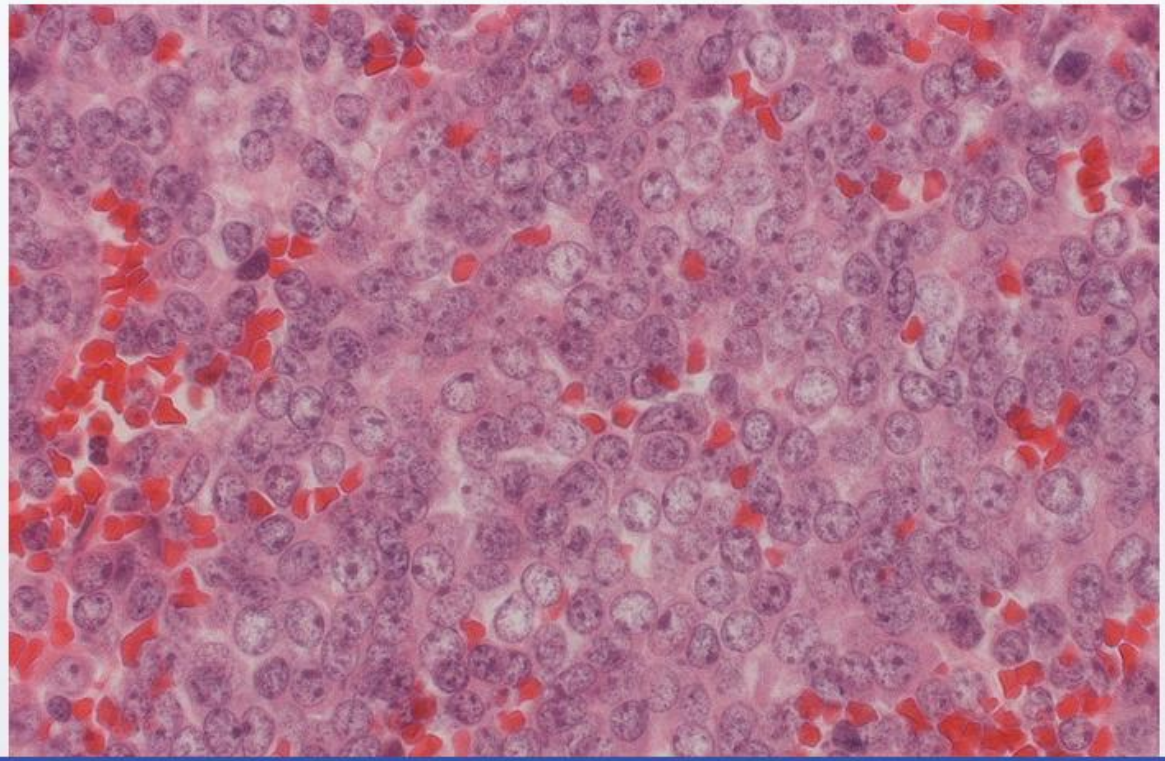
Item 20 of 40
Question Id: 15635

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

A 15-year-old boy is brought to the emergency department due to hemoptysis. He has a history of amputation of the right lower extremity for "bone cancer" in Mexico. Chest imaging reveals a lung mass. Excisional biopsy of the mass shows sheets of uniform, small (slightly larger than lymphocytes), round cells with scant, clear cytoplasm. The cellular deposits are interrupted by vascular fibrous septae, with areas of hemorrhage and an abrupt transition from viable to necrotic cells. A representative sample is shown in the image.



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Settings

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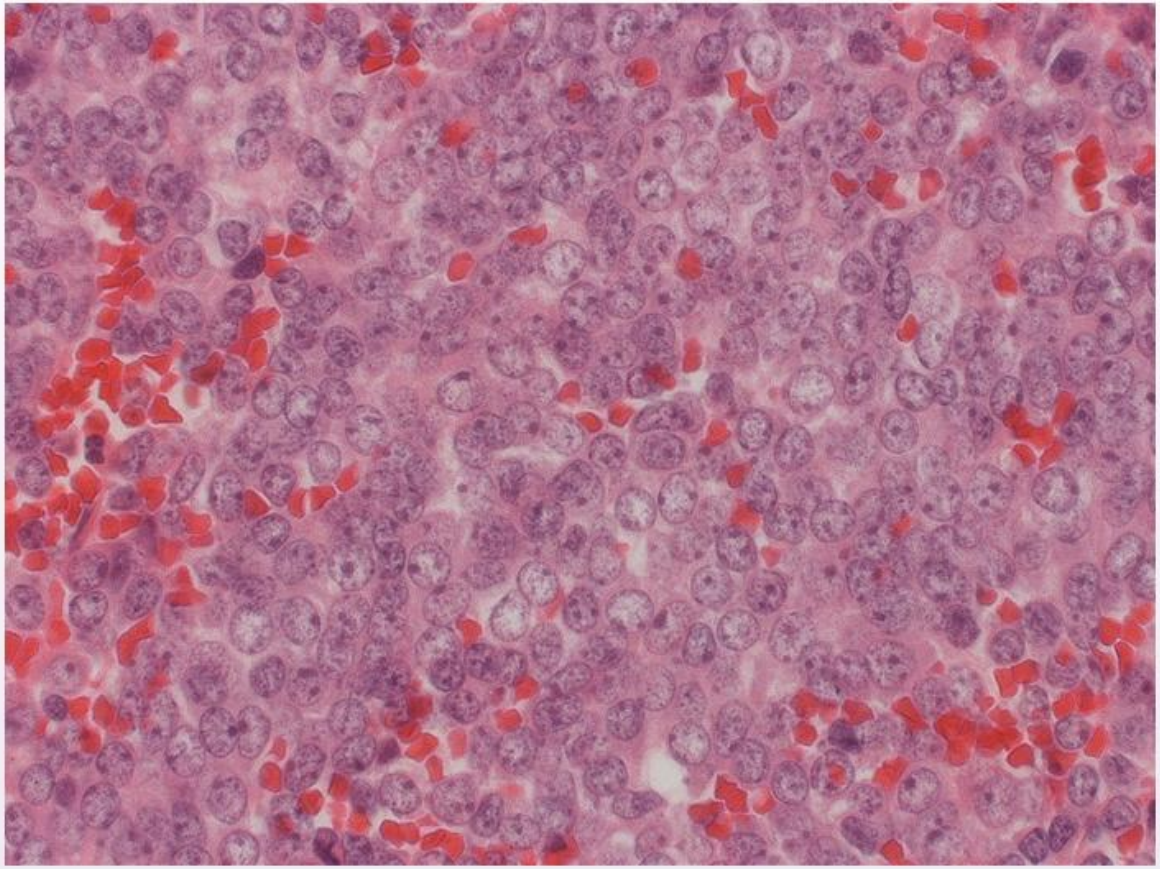
Item 20 of 40
Question Id: 15635

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



Which of the following is the most likely diagnosis?

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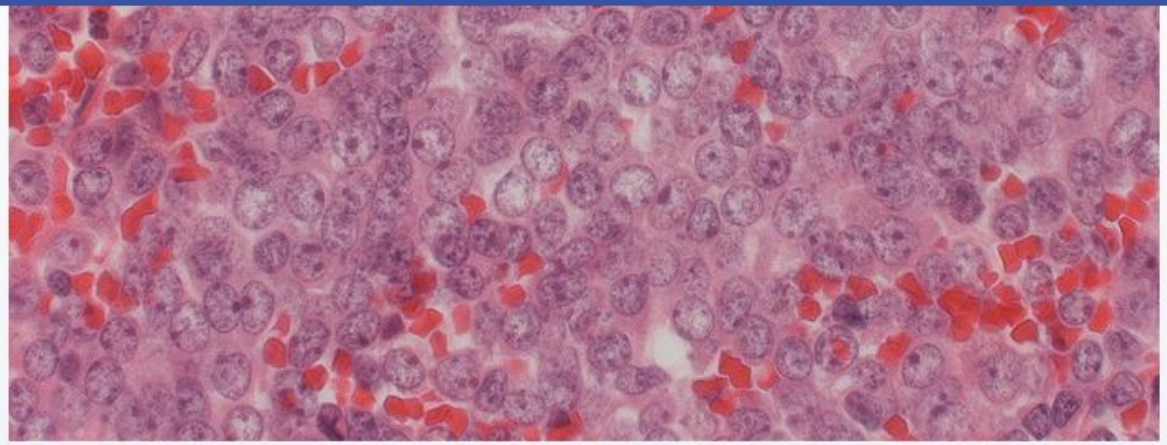
Settings

Item 20 of 40
Question Id: 15635

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



Which of the following is the most likely diagnosis?

- A. Adenocarcinoma
- B. Chondrosarcoma
- C. Ewing sarcoma
- D. Multiple myeloma
- E. Osteosarcoma

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2/10/2019

Settings

Item 20 of 40
Question Id: 15635

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

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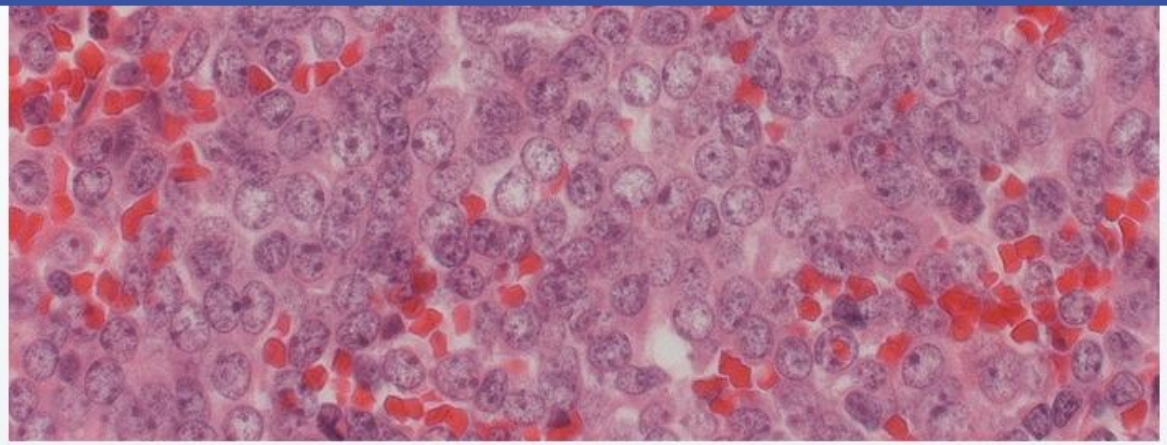

Which of the following is the most likely diagnosis?

- A. Adenocarcinoma [5%]
- B. Chondrosarcoma [8%]
- ✔ C. Ewing sarcoma [61%]
- D. Multiple myeloma [4%]
- E. Osteosarcoma [20%]

Omitted
Correct answer

61%
Answered correctly

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Time Spent

02/04/2019
Last Updated

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Explanation

Ewing sarcoma	
Epidemiology	• Mesenchymal stem cell neoplasm* • Primarily seen in children/young adults • Site of origin: long bones, axial skeleton, or pelvis
Manifestations	• Localized pain & swelling • Early metastases to lungs & other bones (may be subclinical)
Histopathology	• Sheets of uniform, small, round cells separated by fibrous septae • Scant, clear cytoplasm (heavy glycogen content) • Areas of hemorrhage & necrosis • Rare mitotic figures

*Ewing sarcoma was previously thought to be neuroectodermal in origin.

This boy with a history of bone cancer has a lung tumor with sheets of uniform, small, round cells, raising strong suspicion for metastatic **Ewing sarcoma** (ES). ES is the second most common childhood bone malignancy (after osteosarcoma) and typically presents with pain and swelling at the bone tumor site. Spread to the lungs or other tissue can occur in those who don't undergo both resection and chemotherapy.

ES is a primitive, undifferentiated tumor that was originally thought to be neuroectodermal in origin but is now believed to arise from a **mesenchymal stem cell**. Tumor histology typically reveals sheets of **uniform, small, round, cells** with clear, scant cytoplasm separated by **fibrous septae** and patches of necrosis/hemorrhage. This appearance resembles neuroendocrine tumors such as carcinoid and small cell lung cancer. Most cases of ES involve **translocations** of *EWSR1* and *FLI1*.

(Choice A) Adenocarcinoma, the most common primary lung malignancy, often metastasizes to bone. However, histopathology would show

sarcoma (ES). ES is the second most common childhood bone malignancy (after osteosarcoma) and typically presents with pain and swelling at the bone tumor site. Spread to the lungs or other tissue can occur in those who don't undergo both resection and chemotherapy.

ES is a primitive, undifferentiated tumor that was originally thought to be neuroectodermal in origin but is now believed to arise from a **mesenchymal stem cell**. Tumor histology typically reveals sheets of **uniform, small, round, cells** with clear, scant cytoplasm separated by **fibrous septae** and patches of necrosis/hemorrhage. This appearance resembles neuroendocrine tumors such as carcinoid and small cell lung cancer. Most cases of ES involve **translocations** of *EWSR1* and *FLI1*.

(Choice A) Adenocarcinoma, the most common primary lung malignancy, often metastasizes to bone. However, histopathology would show **neoplastic glands** lined by mucin-producing cells.

(Choice B) Chondrosarcoma is an uncommon tumor and typically occurs in the 5th or 6th decade of life. Histology shows **neoplastic chondrocytes** in a hyaline cartilage matrix, usually with small calcifications.

(Choice D) Multiple myeloma is a plasma cell malignancy that is extremely rare in patients age <40. X-ray often shows multiple lytic lesions, osteopenia, and pathologic fractures. The malignant cells have **eccentric nuclei with "clock-face" chromatin**, perinuclear clearing, and abundant basophilic cytoplasm.

(Choice E) Osteosarcoma is the most common primary bone malignancy. Histology shows pleomorphic, spindle-shaped cells that produce **new osteoid** and bone.

Educational objective:
Ewing sarcoma is the second most common malignant bone tumor of childhood (after osteosarcoma). It most commonly involves the lower extremity and pelvis and often metastasizes to the lungs. Histopathology is characterized by uniform, small, round, cells; fibrous septae; and patches of necrosis and hemorrhage.

References

- Pediatric malignant bone tumors: a review and update on current challenges, and emerging drug targets.

Settings

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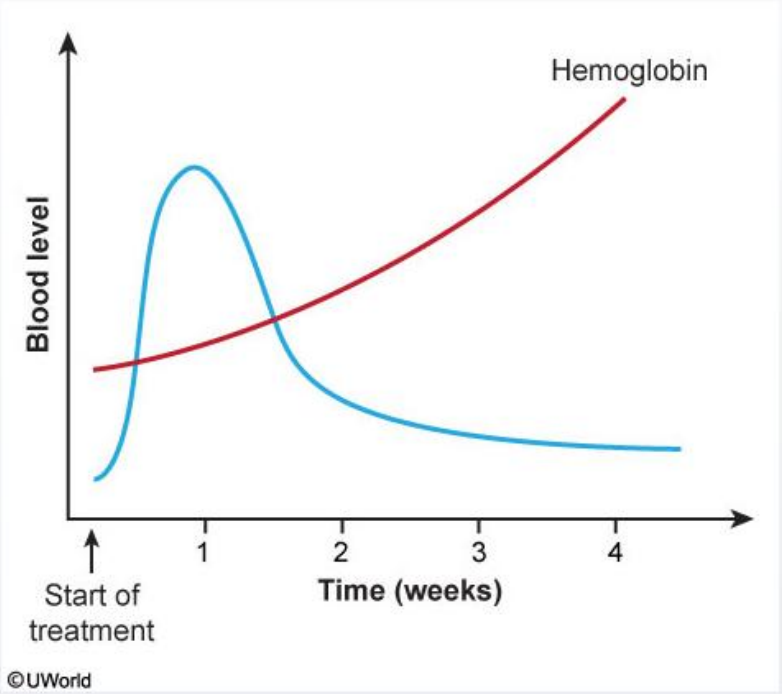
28

Item 21 of 40
Question Id: 1848

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

A 55-year-old man undergoing evaluation for fatigue and exertional dyspnea is diagnosed with macrocytic anemia. Upper gastrointestinal endoscopy is consistent with atrophic gastritis. He is started on intramuscular cyanocobalamin, with the resulting changes shown in the graph below.



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The blue curve most likely corresponds to which of the following parameters?

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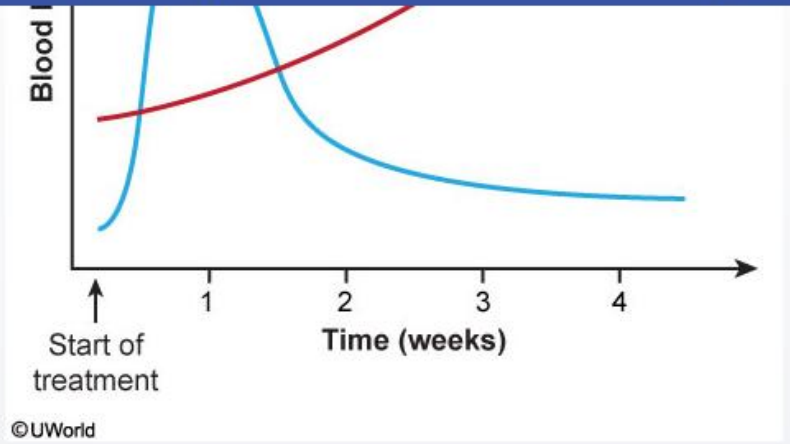
Item 21 of 40
Question Id: 1848

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



The blue curve most likely corresponds to which of the following parameters?

A. Erythrocyte count
B. Gastrin
C. Haptoglobin
D. Methylmalonic acid
E. Reticulocyte count

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2/10/2019

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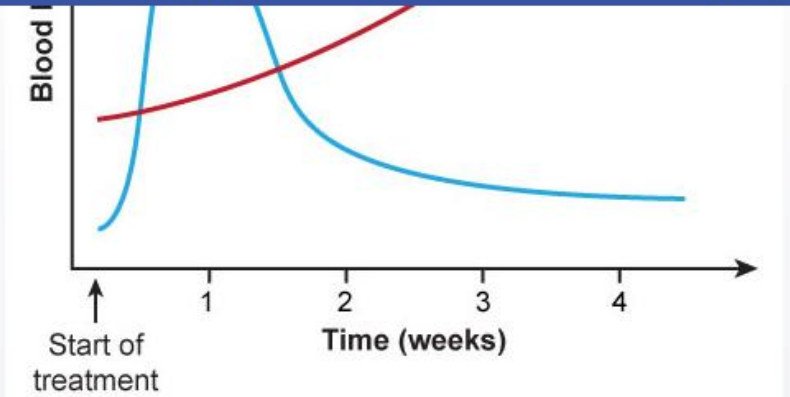
Item 21 of 40
Question Id: 1848

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



The blue curve most likely corresponds to which of the following parameters?

- A. Erythrocyte count [5%]
- B. Gastrin [2%]
- C. Haptoglobin [5%]
- D. Methylmalonic acid [25%]
- ✔ E. Reticulocyte count [60%]

Omitted
Correct answer

60%
Answered correctly

7 Seconds
Time Spent

02/08/2019
Last Updated

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Explanation

The graph shows the treatment response to vitamin B_{12} (cyanocobalamin) in a patient with **vitamin B_{12} deficiency** secondary to atrophic gastritis. Vitamin B_{12} deficiency impairs nucleic acid metabolism, causing delayed nuclear maturation and reduced cell division of erythrocyte precursors in the bone marrow (**megaloblastic anemia**).

Once vitamin B_{12}**replacement therapy** is begun, erythrocyte precursors begin to change from megaloblastic to normoblastic. As the rate of effective erythropoiesis increases, immature erythrocytes (**reticulocytes**) are released from the bone marrow into the bloodstream. The peripheral count of these reticulocytes begins rising within 3 to 4 days and **peaks at around 1 week**, as indicated by the blue curve. The reticulocyte response peaks early during vitamin replacement as the reticulocytes that are initially released are left-shifted and take longer to mature in the circulation than later reticulocytes. However, hemoglobin levels (~1 g/week) are slower to rise, and the anemia typically takes as long as 8 weeks to correct.

(Choice A) The erythrocyte count curve would be expected to follow the contour of the hemoglobin curve as the total red blood cell pool returns to normal levels.

(Choice B) In chronic atrophic gastritis, parietal cell loss results in profound hypochlorhydria, increased serum gastrin levels, and inadequate intrinsic factor production. This patient most likely has elevated gastrin levels that would be unaffected by vitamin B_{12} replacement.

(Choice C) Vitamin B_{12} deficiency causes increased red cell breakdown due to ineffective erythropoiesis, and the resulting release of free hemoglobin leads to a decrease in serum haptoglobin levels. Haptoglobin levels would normalize (increase) with therapy.

(Choice D) Homocysteine and methylmalonic acid levels are elevated in vitamin B_{12} deficiency due to decreased metabolism. In contrast, only homocysteine is elevated in folate deficiency. Vitamin B_{12} replacement would cause a reduction in homocysteine and methylmalonic acid levels. However, the blue curve shows a high initial peak before declining, which is more consistent with the reticulocyte response.

Educational objective:
Atrophic gastritis can result in profound hypochlorhydria, inadequate intrinsic factor production, vitamin B_{12} deficiency, and elevated methylmalonic acid levels. The reticulocyte count increases dramatically once vitamin B_{12} replacement therapy is initiated in an individual with pernicious

the bone marrow (**megaloblastic anemia**).

Once vitamin B_{12} **replacement therapy** is begun, erythrocyte precursors begin to change from megaloblastic to normoblastic. As the rate of effective erythropoiesis increases, immature erythrocytes (**reticulocytes**) are released from the bone marrow into the bloodstream. The peripheral count of these reticulocytes begins rising within 3 to 4 days and **peaks at around 1 week**, as indicated by the blue curve. The reticulocyte response peaks early during vitamin replacement as the reticulocytes that are initially released are left-shifted and take longer to mature in the circulation than later reticulocytes. However, hemoglobin levels (~1 g/week) are slower to rise, and the anemia typically takes as long as 8 weeks to correct.

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(Choice C) Vitamin B_{12} deficiency causes increased red cell breakdown due to ineffective erythropoiesis, and the resulting release of free hemoglobin leads to a decrease in serum haptoglobin levels. Haptoglobin levels would normalize (increase) with therapy.

(Choice D) Homocysteine and methylmalonic acid levels are elevated in vitamin B_{12} deficiency due to decreased metabolism. In contrast, only homocysteine is elevated in folate deficiency. Vitamin B_{12} replacement would cause a reduction in homocysteine and methylmalonic acid levels. However, the blue curve shows a high initial peak before declining, which is more consistent with the reticulocyte response.

Educational objective:
Atrophic gastritis can result in profound hypochlorhydria, inadequate intrinsic factor production, vitamin B_{12} deficiency, and elevated methylmalonic acid levels. The reticulocyte count increases dramatically once vitamin B_{12} replacement therapy is initiated in an individual with pernicious anemia. Hemoglobin and erythrocyte count levels rise more gradually and take up to 8 weeks to normalize.

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28

Item 22 of 40
Question Id: 1793

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

The 59-year-old manager of a small firm comes to the clinic with progressive fatigue and occasional heart palpitations over the last 6 months. She has been under a lot of stress recently due to problems at work. She also has been eating out at restaurants frequently and drinking 2 or 3 cans of beer on the weekends. The patient is postmenopausal and has not noticed any uterine bleeding, dark stools, or bleeding with bowel movements. Her blood hemoglobin level is 8.5 g/dL. Peripheral blood smear reveals pale microcytes. Which of the following is the most likely underlying cause of this patient's abnormal laboratory findings?

A. Drug abuse
B. Hematologic malignancy
C. Hemolysis
D. Liver disease
E. Occult blood loss
F. Poor nutrition

Submit

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2/10/2019

Settings

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28

Item 22 of 40
Question Id: 1793

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

The 59-year-old manager of a small firm comes to the clinic with progressive fatigue and occasional heart palpitations over the last 6 months. She has been under a lot of stress recently due to problems at work. She also has been eating out at restaurants frequently and drinking 2 or 3 cans of beer on the weekends. The patient is postmenopausal and has not noticed any uterine bleeding, dark stools, or bleeding with bowel movements. Her blood hemoglobin level is 8.5 g/dL. Peripheral blood smear reveals pale microcytes. Which of the following is the most likely underlying cause of this patient's abnormal laboratory findings?

- A. Drug abuse [1%]
- B. Hematologic malignancy [3%]
- C. Hemolysis [4%]
- D. Liver disease [3%]
- ✔ E. Occult blood loss [39%]
- F. Poor nutrition [48%]

Omitted
Correct answer
E

39%
Answered correctly

3 Seconds
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Last Updated

Explanation

Fatigue and heart palpitations are common manifestations of all forms of anemia. This patient's peripheral smear findings indicate **hypochromic,**

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E

Explanation

Fatigue and heart palpitations are common manifestations of all forms of anemia. This patient's peripheral smear findings indicate **hypochromic, microcytic anemia**, which **most often** arises in the setting of **iron deficiency**. The primary, and most dangerous if overlooked, mechanism of iron deficiency is **blood loss** and should be excluded first. Women of childbearing age are commonly iron deficient due to menstruation. Older men or postmenopausal women (as this patient) have no physiologic reason to be iron deficient and therefore should be evaluated for blood loss in the **gastrointestinal (GI) tract** (eg, due to malignancy). The blood loss is often **occult**, so the lack of dark or bright red stools in this patient should not rule out GI hemorrhage. Iron studies (including ferritin) should be obtained, and the patient will likely require endoscopic evaluation.

(Choice A) Ingestion of the more commonly abused drugs is not associated with microcytic anemia.

(Choice B) Hematologic malignancies (eg, leukemia, lymphoma, multiple myeloma) tend to be associated with normochromic, normocytic anemia. The decrease in erythropoiesis seen in these patients results from hypersplenism or bone marrow mass replacement by tumor.

(Choice C) Hemolysis often presents with a normochromic, normocytic anemia. Spherocytes or schistocytes are often seen on peripheral blood smear.

(Choice D) The anemia of chronic liver disease is usually normocytic or slightly macrocytic with target cells on the peripheral blood smear. Microcytic anemia occurs in <25% of cases, and most patients only have mild anemia with a hemoglobin level of 10-11 g/dL.

(Choice F) Eating out and drinking a few beers on weekends are not suggestive of the severe malnutrition seen in alcoholics. A normal Western diet provides 6 mg of iron for every 1000 calories, and the recommended intake for individuals age >50 is 8 mg per day. As a result, men and women who are not menstruating, pregnant, or lactating usually have no dietary iron shortage.

Educational objective:
Hypochromic, microcytic anemia is most commonly due to iron deficiency. Blood loss, especially occult loss from the gastrointestinal tract, must

Fatigue and heart palpitations are common manifestations of all forms of anemia. This patient's peripheral smear findings indicate **hypochromic, microcytic anemia**, which **most often** arises in the setting of **iron deficiency**. The primary, and most dangerous if overlooked, mechanism of iron deficiency is **blood loss** and should be excluded first. Women of childbearing age are commonly iron deficient due to menstruation. Older men or postmenopausal women (as this patient) have no physiologic reason to be iron deficient and therefore should be evaluated for blood loss in the **gastrointestinal (GI) tract** (eg, due to malignancy). The blood loss is often **occult**, so the lack of dark or bright red stools in this patient should not rule out GI hemorrhage. Iron studies (including ferritin) should be obtained, and the patient will likely require endoscopic evaluation.

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(Choice B) Hematologic malignancies (eg, leukemia, lymphoma, multiple myeloma) tend to be associated with normochromic, normocytic anemia. The decrease in erythropoiesis seen in these patients results from hypersplenism or bone marrow mass replacement by tumor.

(Choice C) Hemolysis often presents with a normochromic, normocytic anemia. Spherocytes or schistocytes are often seen on peripheral blood smear.

(Choice D) The anemia of chronic liver disease is usually normocytic or slightly macrocytic with target cells on the peripheral blood smear. Microcytic anemia occurs in <25% of cases, and most patients only have mild anemia with a hemoglobin level of 10-11 g/dL.

(Choice F) Eating out and drinking a few beers on weekends are not suggestive of the severe malnutrition seen in alcoholics. A normal Western diet provides 6 mg of iron for every 1000 calories, and the recommended intake for individuals age >50 is 8 mg per day. As a result, men and women who are not menstruating, pregnant, or lactating usually have no dietary iron shortage.

Educational objective:
Hypochromic, microcytic anemia is most commonly due to iron deficiency. Blood loss, especially occult loss from the gastrointestinal tract, must be ruled out in a patient with iron-deficiency anemia.

Settings

Item 23 of 40
Question Id: 1039

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

A 72-year-old man comes to the office due to progressive weakness, fatigue, anorexia, and a 10-kg (22-lb) weight loss over the past 4 months. He says that food doesn't taste as good as it once did, and he feels full after eating only a small amount. The patient has had a morning cough for the past several years and had streaks of blood in his sputum 2 weeks ago. He has a 50-pack-year smoking history. On examination, the patient appears frail with a sunken face and bitemporal wasting. His arms are thin with notable muscle wasting. Lung examination reveals wheezing on the right side. Chest x-ray reveals an irregular right perihilar mass. Which of the following is most likely contributing to this patient's muscle wasting?

- A. Calcium channel autoantibody
- B. Interferon-α
- C. Interleukin-3
- D. Transforming growth factor-β
- E. Tumor necrosis factor-α
- F. Vasopressin

Submit

Block Time Remaining: 00:02:34
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4:14 PM
2/10/2019

Settings

Item 23 of 40
Question Id: 1039

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

A 72-year-old man comes to the office due to progressive weakness, fatigue, anorexia, and a 10-kg (22-lb) weight loss over the past 4 months. He says that food doesn't taste as good as it once did, and he feels full after eating only a small amount. The patient has had a morning cough for the past several years and had streaks of blood in his sputum 2 weeks ago. He has a 50-pack-year smoking history. On examination, the patient appears frail with a sunken face and bitemporal wasting. His arms are thin with notable muscle wasting. Lung examination reveals wheezing on the right side. Chest x-ray reveals an irregular right perihilar mass. Which of the following is most likely contributing to this patient's muscle wasting?

- A. Calcium channel autoantibody [13%]
- B. Interferon-α [5%]
- C. Interleukin-3 [1%]
- D. Transforming growth factor-β [6%]
- ✔ E. Tumor necrosis factor-α [71%]
- F. Vasopressin [1%]

Omitted
Correct answer
E

71%
Answered correctly

2 Seconds
Time Spent

12/18/2018
Last Updated

Explanation

Block Time Remaining: 00:02:35
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2/10/2019

Explanation

Cachexia is a syndrome that encompasses anorexia, malaise, anemia, weight loss, and generalized **wasting** due to underlying systemic disease. Cachexia in this patient is likely a manifestation of the lung **neoplasm** revealed on his chest x-ray. **Tumor necrosis factor-α** (TNF-α) is a cytokine that causes necrosis of some tumors in vitro and produces symptoms of cachexia in experimental animals. TNF-α is also called cachectin and is considered a main mediator of paraneoplastic cachexia (along with interleukin [IL]-1β, and IL-6).

TNF-α is produced by macrophages in response to infection as well as by some neoplastic cells. Its role in cachexia is explained by its influence on the hypothalamus, leading to appetite suppression. It also increases basal metabolic rate. In bacterial infections, TNF-α produces fever (along with IL-1), mediates many of the symptoms of septic shock, and causes hepatic release of acute-phase reactants (eg, C-reactive protein and fibrinogen).

(Choice A) Eaton-Lambert syndrome is a paraneoplastic condition that manifests as progressive, symmetric proximal muscle weakness (rather than wasting) along with ocular and autonomic symptoms. It is due to autoantibodies to voltage-gated calcium channels.

(Choice B) Interferon-α is synthesized by leukocytes and has antiviral as well as anti-tumor activity.

(Choice C) IL-3 is produced by activated CD4+ T_H cells. It stimulates growth and differentiation of myeloid cells.

(Choice D) The main function of transforming growth factor-β is inhibition of the inflammatory response. It decreases T cell proliferation and cytokine production.

(Choice F) Production of vasopressin by some tumors (eg, small cell lung cancer) results in the syndrome of inappropriate antidiuretic hormone secretion.

Educational objective:
Tumor necrosis factor-α is thought to mediate paraneoplastic cachexia in humans by suppressing appetite and increasing basal metabolic rate.

Settings

Item 24 of 40
Question Id: 1759

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

A 62-year-old woman comes to the physician after finding a lump in her breast. Physical examination reveals a firm, immovable, irregularly shaped mass. Mammography is performed and shows a spiculated, calcified lesion that was not seen on prior studies. A tissue biopsy is diagnostic for infiltrating ductal carcinoma. Malignant tumors such as infiltrating ductal carcinoma are typically associated with varying degrees of disordered differentiation and maturation. Which of the following findings is most characteristic of an anaplastic tumor?

A. Brain tumor cells forming giant cells
B. Bronchial epithelial cells producing keratin pearls
C. Colonic tumor cells creating glands
D. Hepatic tumor cells synthesizing bile
E. Skin tumor cells producing keratin pearls

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Block Time Remaining: 00:02:37
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4:14 PM
2/10/2019

Settings

Item 24 of 40
Question Id: 1759

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

A 62-year-old woman comes to the physician after finding a lump in her breast. Physical examination reveals a firm, immovable, irregularly shaped mass. Mammography is performed and shows a spiculated, calcified lesion that was not seen on prior studies. A tissue biopsy is diagnostic for infiltrating ductal carcinoma. Malignant tumors such as infiltrating ductal carcinoma are typically associated with varying degrees of disordered differentiation and maturation. Which of the following findings is most characteristic of an anaplastic tumor?

- ✔ A. Brain tumor cells forming giant cells [49%]
- B. Bronchial epithelial cells producing keratin pearls [31%]
- C. Colonic tumor cells creating glands [7%]
- D. Hepatic tumor cells synthesizing bile [3%]
- E. Skin tumor cells producing keratin pearls [8%]

Omitted
Correct answer
A

49%
Answered correctly

3 Seconds
Time Spent

12/09/2018
Last Updated

Explanation

Well differentiated (low-grade) tumors contain neoplastic cells that are morphologically and architecturally similar to normal cells in the tissue of origin. In contrast, poorly differentiated (high-grade) tumors contain neoplastic cells that lack most of the characteristic features of the original tissue. Neoplasms that contain cells in the midst of this spectrum are termed moderately differentiated (medium-grade). Neoplastic cells that demonstrate a complete lack of differentiation are termed anaplastic.

Block Time Remaining: 00:02:38
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Well differentiated (low-grade) tumors contain neoplastic cells that are morphologically and architecturally similar to normal cells in the tissue of origin. In contrast, poorly differentiated (high-grade) tumors contain neoplastic cells that lack most of the characteristic features of the original tissue. Neoplasms that contain cells in the midst of this spectrum are termed moderately differentiated (medium-grade). Neoplastic cells that demonstrate a complete lack of differentiation are termed anaplastic.

Anaplastic tumors typically demonstrate the following features:

1. Loss of cell polarity with complete disruption of normal tissue architecture; cells coalesce into sheets or islands in a disorganized, infiltrative fashion (**example**, compare to **normal**)
2. Significant variation in the shape and size of cells (cellular pleomorphism) and nuclei (**nuclear pleomorphism**)
3. Disproportionately large nuclei (high nucleus-to-cytoplasm ratio) that are often deep-staining (hyperchromatic) with abundant, coarsely-clumped chromatin and large nucleoli (**example**)
4. Numerous, often abnormal, **mitotic figures**
5. **Giant, multinucleated tumor cells** **(Choice A)**

(Choices B and E) The production of keratin pearls by skin tumor cells is an example of dysplasia (ie, disordered growth). The fact that they produce keratin means that the tumor cells are well differentiated. Bronchial epithelial cells can also produce keratin pearls after undergoing a phenotypic switch from columnar epithelium to squamous epithelium. The process of switching from one differentiated cell type to another is known as metaplasia and often occurs in response to irritants (eg, tobacco smoke or gastric acid).

(Choices C and D) Cells in the colon normally form goblet cell-containing glands and cells in hepatic tissue normally synthesize bile. Therefore, the described tumor cells would be well-differentiated, not anaplastic.

Educational objective:
Undifferentiated (anaplastic) tumors bear no resemblance to the tissue of origin. They are composed of pleomorphic cells with large, hyperchromatic nuclei that grow in a disorganized fashion. Anaplastic tumors may also contain numerous, abnormal mitoses and giant tumor cells.

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Item 24 of 40
Question Id: 1759

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

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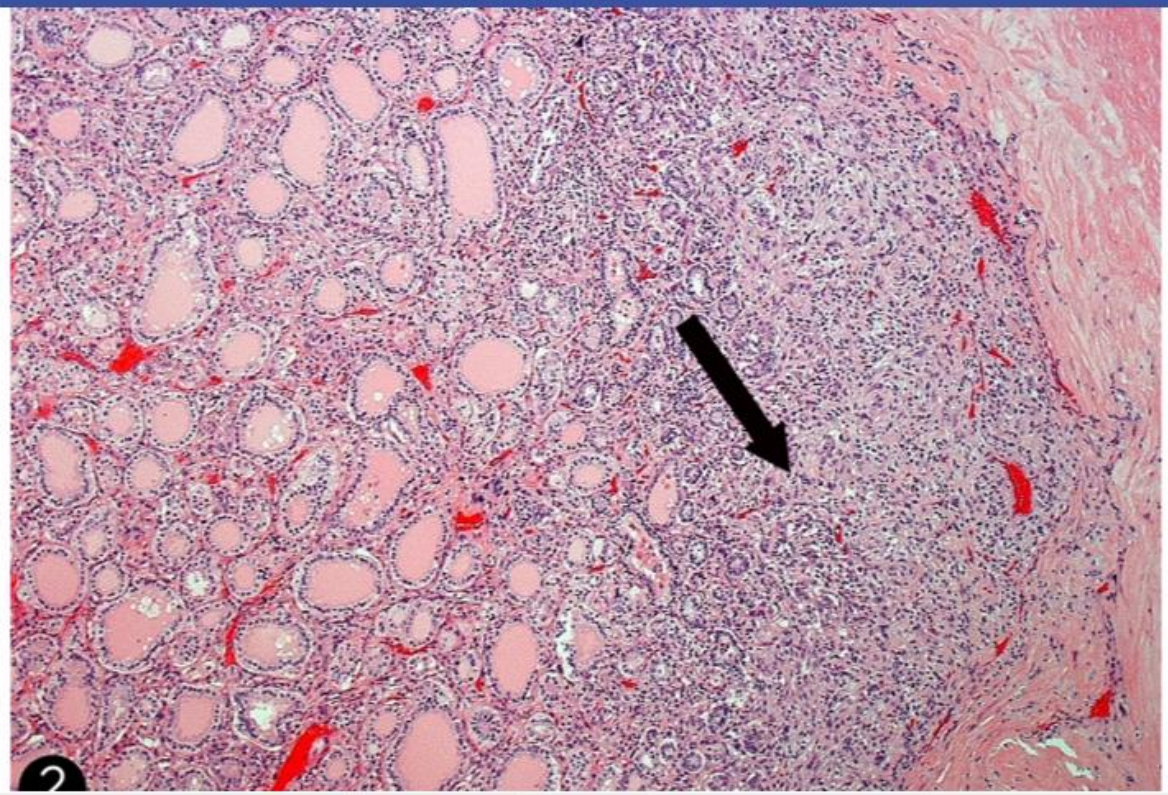

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Item 24 of 40
Question Id: 1759

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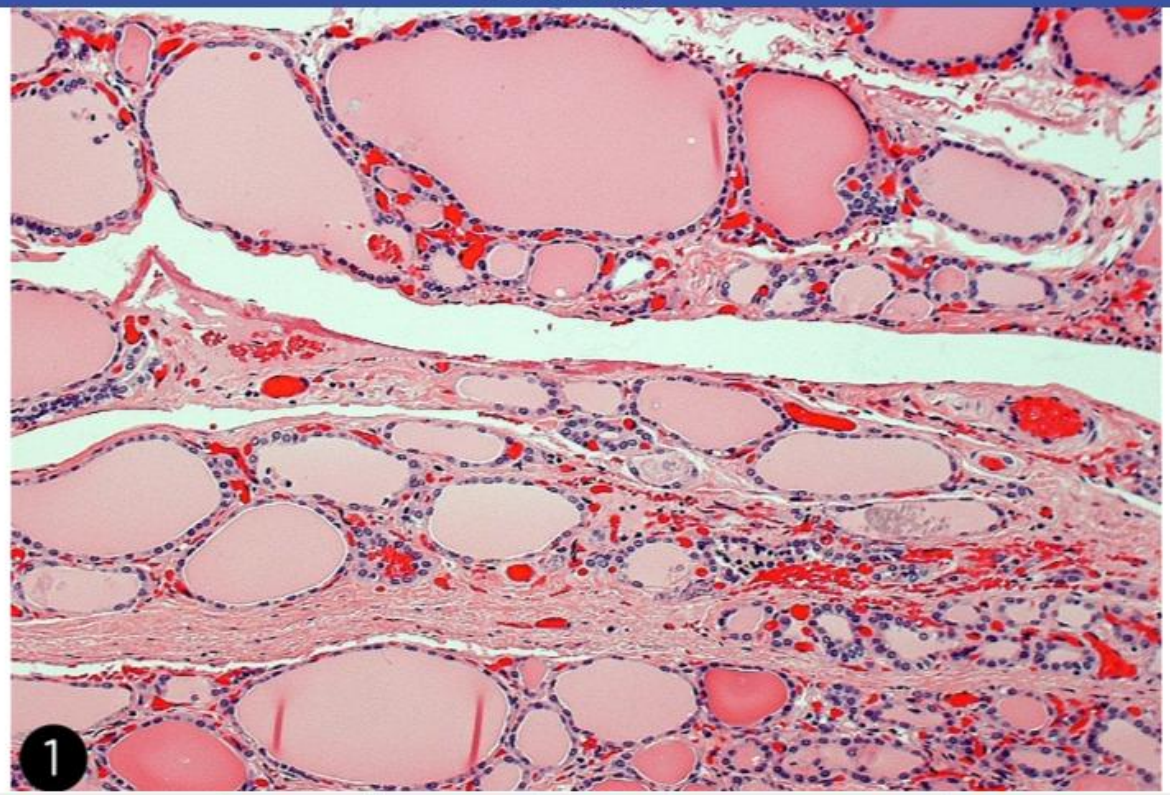

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Item 24 of 40
Question Id: 1759

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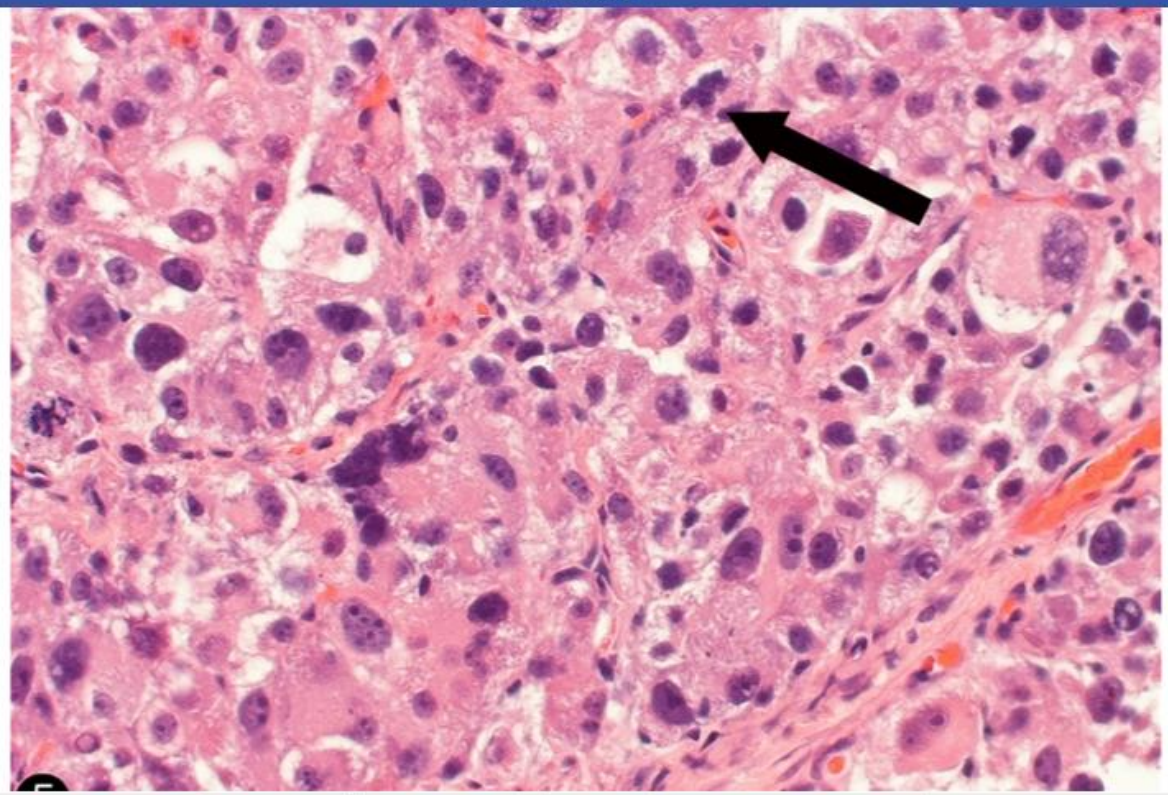

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Item 24 of 40
Question Id: 1759

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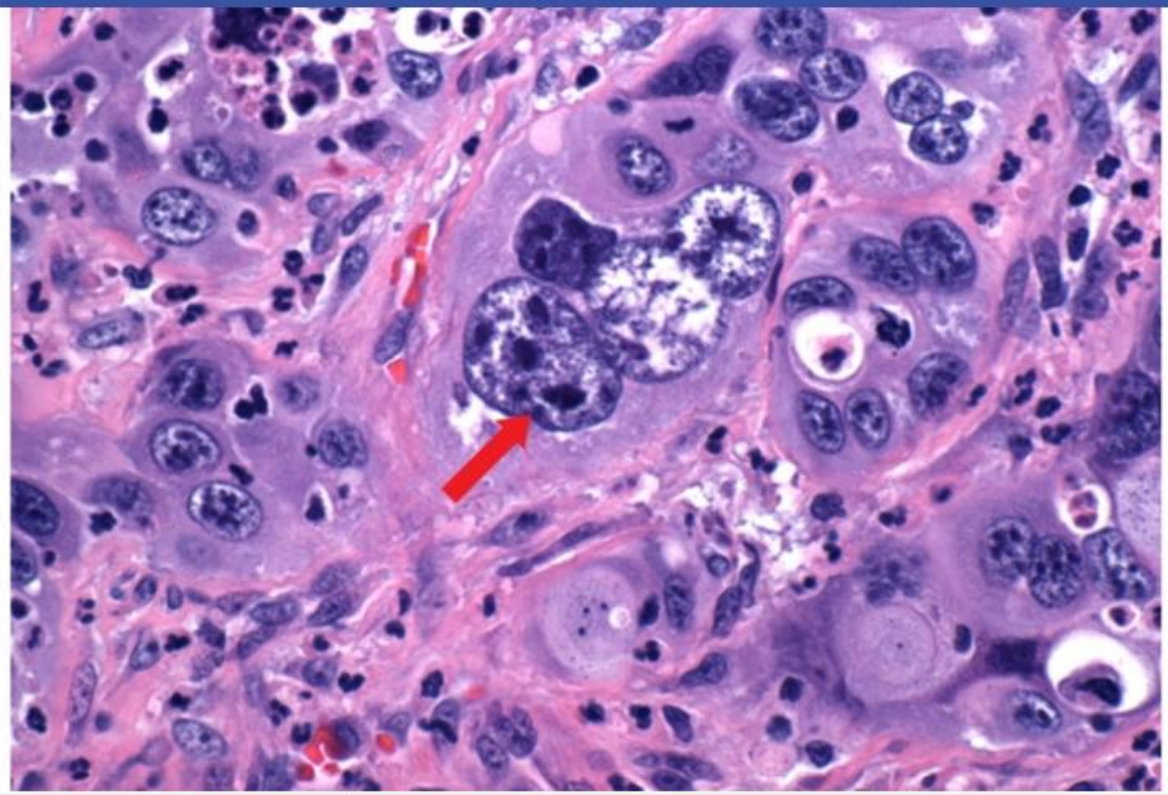

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Item 24 of 40
Question Id: 1759

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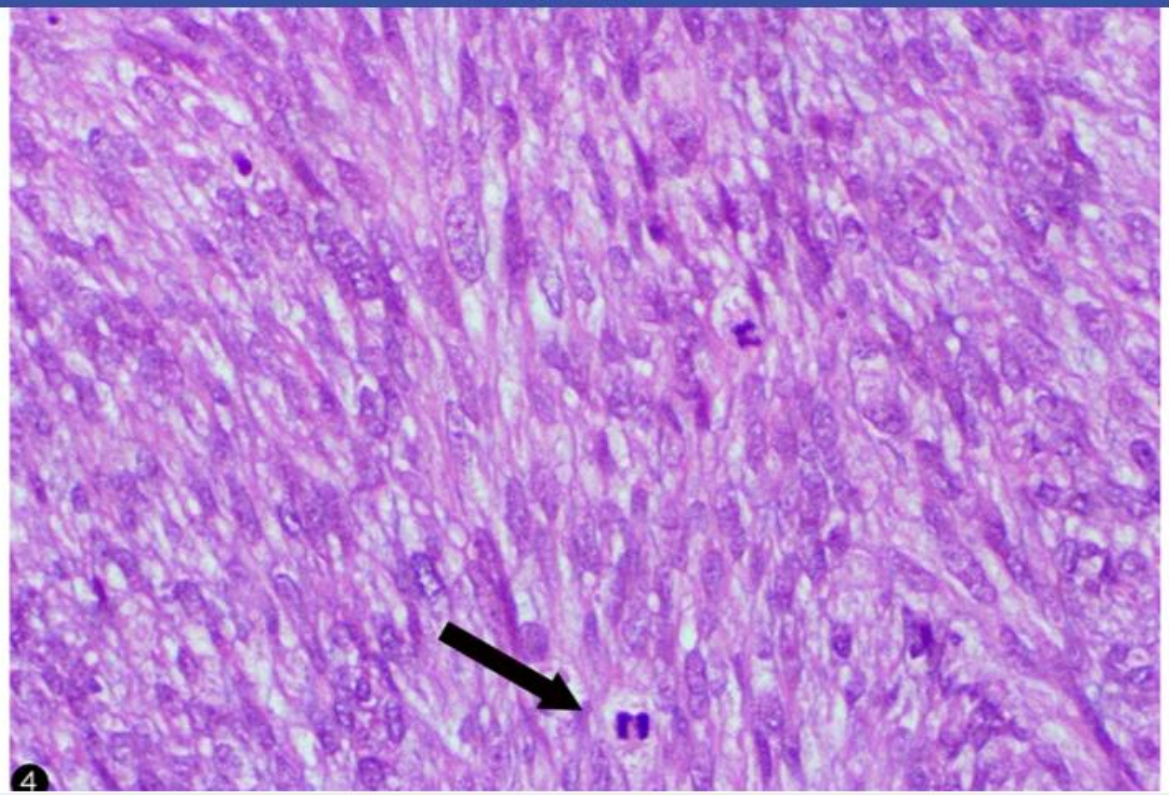

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Item 24 of 40
Question Id: 1759

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

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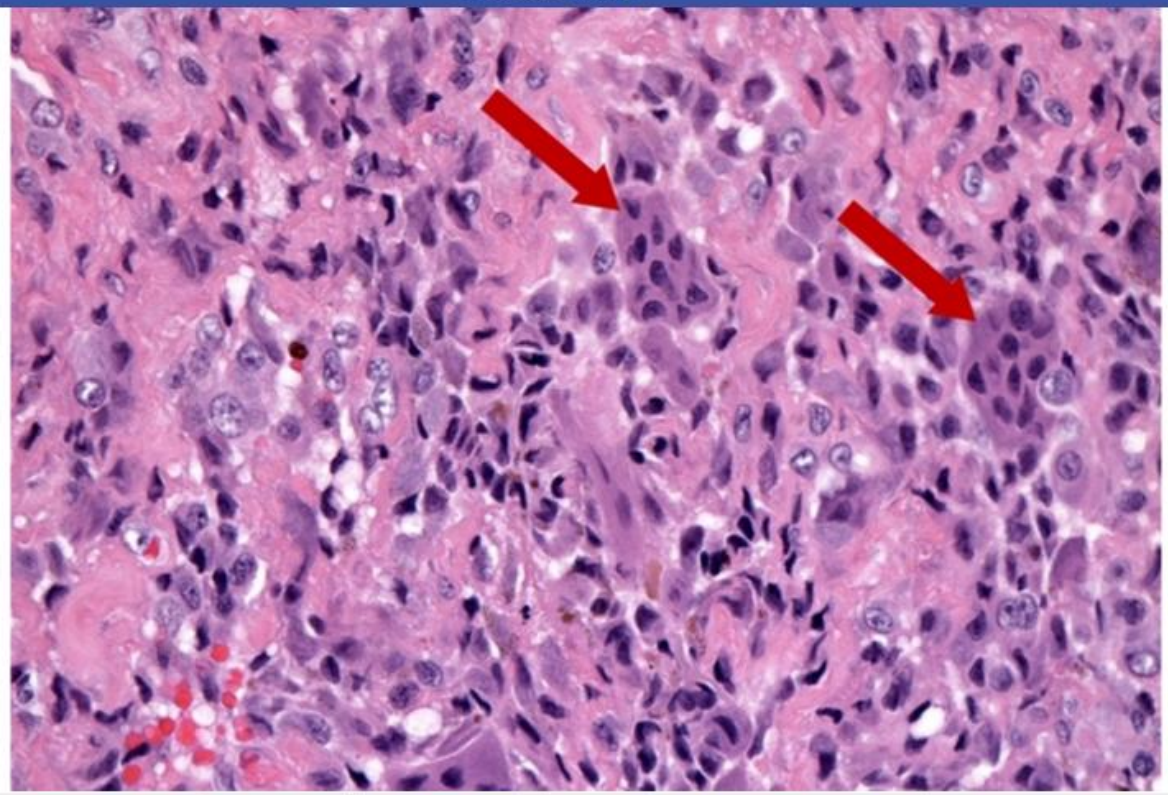

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Item 25 of 40
Question Id: 1160

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

A 54-year-old male presents with an enlarged left-sided supraclavicular lymph node. The node is painless and stony hard on palpation. The node biopsy reveals anaplastic cells that stain positive for keratin. Which of the following is the most likely origin of the cells detected on the biopsy?

A. Lymphocytes
B. Epithelial surfaces
C. Muscle tissue
D. Endothelium
E. Glial cells

Submit

Block Time Remaining: 00:02:39
TUTOR

10 | Feedback | Suspend | End Block

4:15 PM
2/10/2019

Settings

Item 25 of 40
Question Id: 1160

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

A 54-year-old male presents with an enlarged left-sided supraclavicular lymph node. The node is painless and stony hard on palpation. The node biopsy reveals anaplastic cells that stain positive for keratin. Which of the following is the most likely origin of the cells detected on the biopsy?

- A. Lymphocytes [2%]
- ✔ B. Epithelial surfaces [88%]
- C. Muscle tissue [1%]
- D. Endothelium [5%]
- E. Glial cells [1%]

Omitted
Correct answer
B

88%
Answered correctly

3 Seconds
Time Spent

08/27/2018
Last Updated

Explanation

Keratins are a broad group of intermediate filaments present in epithelial cells. Immunohistochemistry stains that employ keratin markers are used by pathologists in the identification of poorly differentiated tumors or tumors with an unclear site of origin. Tumors that stain positive for keratin include carcinomas, mesotheliomas, thymomas, various sarcomas, trophoblastic tumors, and desmoplastic small round cell tumors.

(Choice A) Lymphocytes can be identified immunohistochemically with a special stain for the pan T cell marker CD3, among others.

Block Time Remaining: 00:02:41
TUTOR

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4:15 PM
2/10/2019

E. Glial cells [1%]

Omitted
Correct answer
B

88%
Answered correctly

3 Seconds
Time Spent

08/27/2018
Last Updated

Explanation

Keratins are a broad group of intermediate filaments present in epithelial cells. Immunohistochemistry stains that employ keratin markers are used by pathologists in the identification of poorly differentiated tumors or tumors with an unclear site of origin. Tumors that stain positive for keratin include carcinomas, mesotheliomas, thymomas, various sarcomas, trophoblastic tumors, and desmoplastic small round cell tumors.

(Choice A) Lymphocytes can be identified immunohistochemically with a special stain for the pan T cell marker CD3, among others.

(Choice C) Muscle tissue can be identified immunohistochemically with special stains for smooth muscle actin, caldesmon, or desmin, among others.

(Choice D) Endothelium can be identified immunohistochemically with special stains for CD34 and von Willebrand's factor, among others.

(Choice E) Glial cells can be identified immunohistochemically with a special stain for glial fibrillary acidic protein.

Educational Objective:
Keratin is a marker of epithelial cell origin.

Settings

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28

Item 26 of 40
Question Id: 1941

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

A 34-year-old obese man presents to your office complaining of fatigue, daytime sleepiness and occasional headaches. When you inquire about his sleeping habits, he reports that he sleeps in a separate room from his wife because she finds his snoring annoying. On physical examination, his blood pressure is 160/90 mmHg and his heart rate is 80/min. His abdomen is soft and non-tender, his liver span is 9 cm, and his spleen is not palpable. Laboratory findings are:

Hematocrit	57%
WBC count	9,000/mm^3
Platelets	190,000/mm^3

Decreased oxygen delivery to which of the following organs is responsible for his increased hematocrit?

- A. Brain
- B. Liver
- C. Spleen
- D. Bone marrow
- E. Lungs
- F. Kidneys

Submit

Block Time Remaining: 00:02:42
TUTOR

10 | Feedback | Suspend | End Block

4:15 PM
2/10/2019

Settings

Item 26 of 40
Question Id: 1941

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

A 34-year-old obese man presents to your office complaining of fatigue, daytime sleepiness and occasional headaches. When you inquire about his sleeping habits, he reports that he sleeps in a separate room from his wife because she finds his snoring annoying. On physical examination, his blood pressure is 160/90 mmHg and his heart rate is 80/min. His abdomen is soft and non-tender, his liver span is 9 cm, and his spleen is not palpable. Laboratory findings are:

Hematocrit	57%
WBC count	9,000/mm^3
Platelets	190,000/mm^3

Decreased oxygen delivery to which of the following organs is responsible for his increased hematocrit?

- A. Brain [9%]
- B. Liver [2%]
- C. Spleen [2%]
- D. Bone marrow [3%]
- E. Lungs [7%]
- ✔ F. Kidneys [74%]

Omitted
Correct answer
F

74%
Answered correctly

3 Seconds
Time Spent

02/06/2019
Last Updated

Block Time Remaining: 00:02:44
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4:16 PM
2/10/2019

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28

Explanation

This patient most likely has obstructive sleep apnea (OSA), a disease characterized by recurrent episodes of asphyxia during sleep, often up to 500 times per night. In patients with OSA, peritubular cells in the renal cortex sense hypoxia and respond by releasing erythropoietin into the bloodstream. (Deficient erythropoietin production is the reason why many patients with chronic kidney disease develop anemia.) Erythropoietin stimulates erythrocyte production by binding to erythropoietin receptors on erythrocyte precursors in the bone marrow. This response is responsible for the secondary polycythemia that occurs in patients with chronic hypoxia secondary to OSA, COPD, right-to-left shunts and high altitude.

(Choice A) Brain doesn't produce erythropoietin.

(Choice B) The liver is the major site of erythropoietin production in the fetus.

(Choice C) The spleen is the major site of destruction of aged or defective erythrocytes. The spleen and liver are potential sites of extramedullary hematopoiesis.

(Choice D) Erythropoietin released by the kidneys circulates to the bone marrow where it stimulates erythroid progenitor cells to synthesize more erythrocytes.

(Choice E) Lung stretch receptors sense distention of the lungs. Stimulation of these receptors decreases the respiratory rate.

Educational Objective:
Renal cortical cells sense hypoxia and respond by synthesizing and releasing erythropoietin. Erythropoietin stimulates the production of erythrocytes in the bone marrow.

Settings

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28

Item 27 of 40
Question Id: 1859

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

A 4-year-old male dies in the hospital from overwhelming infection. Autopsy findings include bone deformities and hepatosplenomegaly. Clumps of erythroid precursor cells are found in the liver and the spleen. The presence of these precursor cells is most likely related to which of the following conditions?

A. Frequent transfusions
B. Immune deficiency
C. Erythropoietin deficiency
D. Chronic hemolysis
E. Iron deficiency
F. Cyanocobalamin deficiency
G. Portal hypertension

Submit

Block Time Remaining: 00:02:46
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10 | Feedback | Suspend | End Block

4:16 PM
2/10/2019

Settings

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Item 27 of 40
Question Id: 1859

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

A 4-year-old male dies in the hospital from overwhelming infection. Autopsy findings include bone deformities and hepatosplenomegaly. Clumps of erythroid precursor cells are found in the liver and the spleen. The presence of these precursor cells is most likely related to which of the following conditions?

A. Frequent transfusions [7%]
B. Immune deficiency [11%]
C. Erythropoietin deficiency [8%]
✔ D. Chronic hemolysis [66%]
E. Iron deficiency [2%]
F. Cyanocobalamin deficiency [2%]
G. Portal hypertension [0%]

Omitted
Correct answer
D

66%
Answered correctly

4 Seconds
Time Spent

02/06/2019
Last Updated

Explanation

The presence of erythroid precursor cells in the liver and spleen is indicative of extramedullary hematopoiesis, a condition characterized by

Block Time Remaining: 00:02:48
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10 | Feedback | Suspend | End Block

4:16 PM
2/10/2019

Explanation

The presence of erythroid precursor cells in the liver and spleen is indicative of extramedullary hematopoiesis, a condition characterized by erythropoietin-stimulated, hyperplastic marrow cell invasion of extramedullary organs. Extramedullary hematopoiesis is most frequently caused by severe chronic hemolytic anemias, such as β-thalassemia (which the child depicted here may well have had).

Extramedullary hematopoiesis can cause a range of skeletal abnormalities. The expanding mass of progenitor cells in the bone marrow thins the bony cortex and impairs bone growth. Pathologic fractures are common in the most symptomatic of children. Maxillary overgrowth and frontal bossing are associated with the characteristic "chipmunk facies" observed in the pediatric population.

(Choice A) Red blood cell transfusions limit extramedullary hematopoiesis by reducing hypoxia.

(Choice B) Immune deficiencies are not frequently associated with red blood cell hemolysis.

(Choice C) Erythropoietin deficiency is observed in patients with chronic renal disease and would be associated with anemia, not extramedullary hematopoiesis.

(Choice E) Iron deficiency results in a relative depression of erythropoietic activity and is not associated with extramedullary hematopoiesis.

(Choice F) Cyanocobalamin (vitamin B_{12}) deficiency causes a megaloblastic anemia that is not associated with extramedullary hematopoiesis.

(Choice G) Intrahepatic extramedullary hematopoiesis can cause portal hypertension, and portal hypertension can cause hepatosplenomegaly. The reverse is not true, however.

Educational Objective:
The presence of erythroid precursors in organs such as the liver and spleen is indicative of extramedullary hematopoiesis, a condition characterized by erythropoietin-stimulated, hyperplastic marrow cell invasion of extramedullary organs. Extramedullary hematopoiesis is most frequently caused by severe chronic hemolytic anemias, such as β-thalassemia.

A 5-year-old boy is brought to the office by his parents who say that he "looks yellow" and has been uncharacteristically tired lately. He has had upper respiratory tract infection symptoms for the past 3 days, including cough, rhinorrhea, sneezing, and sore throat. The parents say that "a lot of kids at daycare have been sick lately." The patient has no prior medical problems. He is consistently at the 50th percentile for height and weight. He takes no medications, and his immunizations are up to date. Pallor, scleral icterus, and palpable splenomegaly are seen on examination. Laboratory results are as follows:

Complete blood count	
Hemoglobin	9 g/dL
Reticulocytes	10.8%
Platelets	218,000/mm^3
Leukocytes	7500/mm^3
Liver studies	
Total bilirubin	3 mg/dL
Direct bilirubin	0.8 mg/dL
Alkaline phosphatase	95 U/L
Aspartate aminotransferase (AST)	18 U/L
Alanine aminotransferase (ALT)	15 U/L

The patient recovers spontaneously after a few weeks. Peripheral smear of the boy's blood after recovery is shown in the **exhibit**. Which of the following is the most likely cause of this patient's condition?

Leukocytes	7500/mm³

Liver studies

Total bilirubin	3 mg/dL
Direct bilirubin	0.8 mg/dL
Alkaline phosphatase	95 U/L
Aspartate aminotransferase (AST)	18 U/L
Alanine aminotransferase (ALT)	15 U/L

The patient recovers spontaneously after a few weeks. Peripheral smear of the boy's blood after recovery is shown in the **exhibit**. Which of the following is the most likely cause of this patient's condition?

- A. Glucose-6-phosphate dehydrogenase enzyme deficiency
- B. Imbalance between alpha and beta globin chain production
- C. Nuclear maturation defect due to defective DNA synthesis
- D. Polymerization of hemoglobin within red blood cells
- E. Red blood cell membrane cytoskeleton abnormalities

Submit

Leukocytes	7500/mm³

Liver studies

Total bilirubin	3 mg/dL
Direct bilirubin	0.8 mg/dL
Alkaline phosphatase	95 U/L
Aspartate aminotransferase (AST)	18 U/L
Alanine aminotransferase (ALT)	15 U/L

The patient recovers spontaneously after a few weeks. Peripheral smear of the boy's blood after recovery is shown in the **exhibit**. Which of the following is the most likely cause of this patient's condition?

- A. Glucose-6-phosphate dehydrogenase enzyme deficiency [20%]
- B. Imbalance between alpha and beta globin chain production [5%]
- C. Nuclear maturation defect due to defective DNA synthesis [5%]
- D. Polymerization of hemoglobin within red blood cells [5%]
- ✔ E. Red blood cell membrane cytoskeleton abnormalities [63%]

Omitted
Correct answer

63%
Answered correctly

10 Seconds
Time Spent

01/11/2019
Last Updated

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Explanation

Hereditary spherocytosis	
Epidemiology	• Autosomal dominant inheritance (~75%) • Northern European descent
Clinical presentation	• Hemolytic anemia • Jaundice • Splenomegaly
Laboratory findings	• ↑ **Mean corpuscular hemoglobin concentration** • **Spherocytes** on peripheral smear • Negative Coombs test • ↑ Osmotic fragility on **acidified glycerol lysis test**
Treatment	• Splenectomy
Complications	• Pigmented gallstones • Aplastic crises from parvovirus B19 infection

This patient's peripheral smear shows **spherocytes**, which are approximately two-thirds of the diameter of normal RBCs, more densely hemoglobinized at the periphery, and often lack a zone of central pallor. This patient's presentation is consistent with hereditary spherocytosis

This patient's peripheral smear shows **spherocytes**, which are approximately two-thirds of the diameter of normal RBCs, more densely hemoglobinized at the periphery, and often lack a zone of central pallor. This patient's presentation is consistent with hereditary spherocytosis (HS), an autosomal dominant hemolytic anemia due to a **red blood cell (RBC) membrane defect**. The mutation in HS most often affects the plasma-membrane scaffolding proteins **spectrin** and **ankyrin**. Without this scaffolding, spherocytes are less deformable than normal RBCs and are prone to sequestration and subsequent accelerated **destruction in the spleen**.

Clinical manifestations include **hemolytic anemia, jaundice** (increased RBC destruction results in greater bilirubin production), and **splenomegaly** (spherocytes have difficulty passing through the cords of Billroth and accumulate in the spleen). Infections can trigger hemolysis and lead to an acute hemolytic crisis, as seen in this patient. Age of diagnosis varies considerably, but many patients have jaundice and fatigue in times of increased hemolysis in the setting of viral infections.

(Choice A) Glucose-6-phosphate dehydrogenase (G6PD) enzyme deficiency anemia usually follows oxidative stress. Common triggers include drugs (sulfonamide or antimalarial agents), fava beans, and infections (viral hepatitis, pneumonia, or typhoid). Peripheral smears of G6PD deficiency anemia show **bite cells** and Heinz bodies, not spherocytes.

(Choice B) An imbalance between alpha globin and beta globin chain production results in thalassemia. In this patient, the peripheral smear has no morphologic variants associated with thalassemia, such as **target cells** or hypochromic microcytes.

(Choice C) A nuclear maturation defect due to defective DNA synthesis is the pathophysiologic mechanism of megaloblastic anemia, which is most commonly caused by vitamin B_{12} and folic acid deficiencies. In this patient's peripheral smear, small spherocytes are primarily seen and not the enlarged **oval cells** and hypersegmented neutrophils of megaloblastic anemia.

(Choice D) Polymerization of hemoglobin occurs in sickle cell anemia. A missense mutation in the beta globin chain leads to the production of hemoglobin S, which has the capacity to polymerize in deoxygenated states. This polymerization leads to red blood cell membrane injury and deformation to a **"sickle" shape** seen on peripheral smear.

Educational objective:
Hereditary spherocytosis results from red cell cytoskeleton abnormalities, most commonly spectrin and ankyrin. Hemolytic anemia, jaundice, and

(Choice A) Glucose-6-phosphate dehydrogenase (G6PD) enzyme deficiency anemia usually follows oxidative stress. Common triggers include drugs (sulfonamide or antimalarial agents), fava beans, and infections (viral hepatitis, pneumonia, or typhoid). Peripheral smears of G6PD deficiency anemia show **bite cells** and Heinz bodies, not spherocytes.

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Educational objective:
Hereditary spherocytosis results from red cell cytoskeleton abnormalities, most commonly spectrin and ankyrin. Hemolytic anemia, jaundice, and splenomegaly are classic manifestations. Spherocytes are seen on peripheral blood smear.

References

- Disorders of red cell membrane.
- Red cell membrane: past, present, and future.
- Abnormalities of the erythrocyte membrane.

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Item 28 of 40
Question Id: 889

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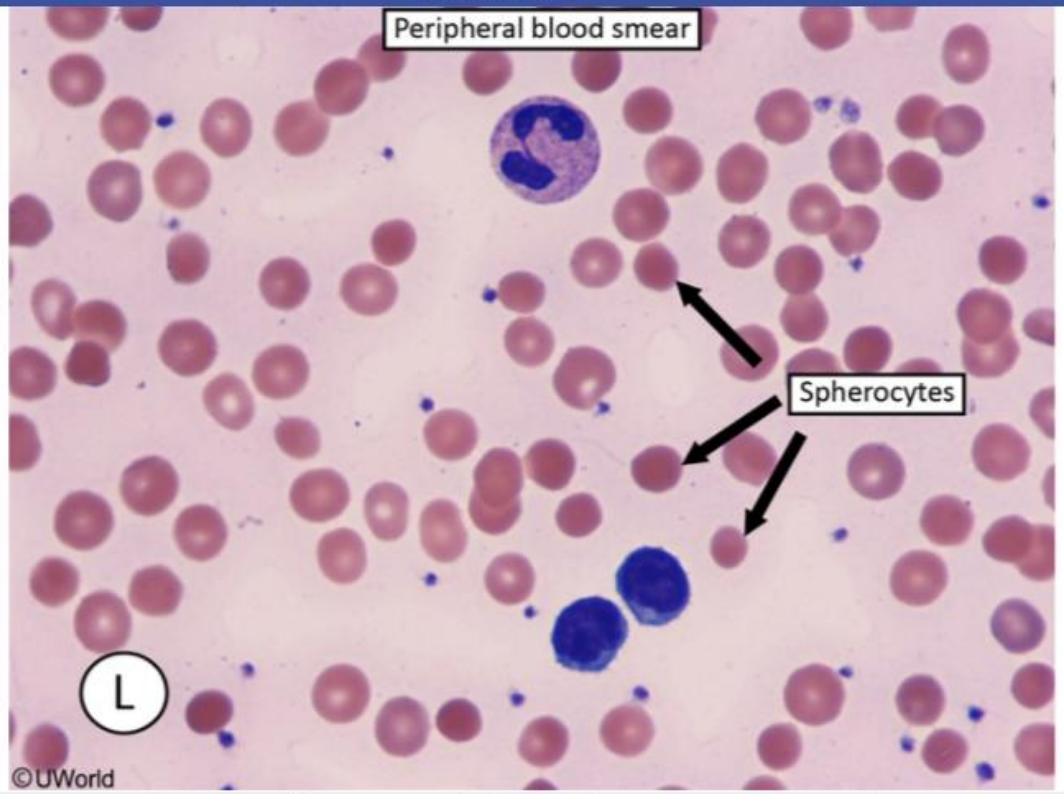
Clinical

- Jaundice

Exhibit Display



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drugs (sulfonamide or antimalarial agents), fava beans, and infections (viral hepatitis, pneumonia, or typhoid). Peripheral smears of G6PD

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Item 29 of 40
Question Id: 1797

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Individuals who demonstrate increased activity of a specific intracellular enzyme are more susceptible to developing benz(o)pyrene-induced lung cancer. Which one of the following enzymes is most likely overactive in these patients?

A. Glutathione-S-transferase
B. Glucuronide transferase
C. Microsomal monooxygenase
D. Mitochondrial cytochrome oxidase
E. Superoxide dismutase

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Item 29 of 40
Question Id: 1797

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Individuals who demonstrate increased activity of a specific intracellular enzyme are more susceptible to developing benz(o)pyrene-induced lung cancer. Which one of the following enzymes is most likely overactive in these patients?

A. Glutathione-S-transferase [15%]
B. Glucuronide transferase [8%]
✔ C. Microsomal monooxygenase [23%]
D. Mitochondrial cytochrome oxidase [25%]
E. Superoxide dismutase [27%]

Omitted
Correct answer
C

23%
Answered correctly

3 Seconds
Time Spent

02/06/2019
Last Updated

Explanation

Many chemicals can induce cancer in humans, with most such substances existing in an inactive, pro-carcinogenic state. Pro-carcinogens are metabolized by cytochrome P450 monooxygenase, an enzyme system present in hepatic microsomes and the endoplasmic reticula of varied other tissues. Cytochrome P450 monooxygenase metabolizes steroids, alcohol, toxins, and other foreign substances by rendering them soluble and easier to excrete. Unfortunately, this metabolic processing also converts pro-carcinogens into carcinogens capable of causing mutations in human DNA.

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Explanation

Many chemicals can induce cancer in humans, with most such substances existing in an inactive, pro-carcinogenic state. Pro-carcinogens are metabolized by cytochrome P450 monooxygenase, an enzyme system present in hepatic microsomes and the endoplasmic reticula of varied other tissues. Cytochrome P450 monooxygenase metabolizes steroids, alcohol, toxins, and other foreign substances by rendering them soluble and easier to excrete. Unfortunately, this metabolic processing also converts pro-carcinogens into carcinogens capable of causing mutations in human DNA.

(Choice A) Glutathione-S-transferase is involved in the detoxification of some chemical carcinogens. Unlike cytochrome P450 oxidase, this enzyme converts toxic substances into inactive metabolites.

(Choice B) Glucuronide transferase converts bilirubin into soluble bilirubin diglucuronide in the hepatocytes. This enzyme is not involved in the metabolism of chemical carcinogens.

(Choice D) Mitochondrial cytochrome oxidase (cytochrome a+a3) is a component of the electron transport chain that reacts with molecular oxygen to produce water. This enzyme is not involved in the metabolism of chemical carcinogens.

(Choice E) Superoxide dismutase converts superoxide into oxygen and hydrogen peroxide during phagocytosis. This enzyme is not involved in the metabolism of chemical carcinogens.

Educational Objective:
Most chemical carcinogens enter the body in an inactive state (ie, as pro-carcinogens). These pro-carcinogens are converted into active metabolites by the cytochrome P450 oxidase system. Individual susceptibility to chemical carcinogens depends on the activity of these P450 enzymes, which is genetically determined.

Settings

Item 30 of 40
Question Id: 11456

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

A 24-year-old previously healthy woman comes to the hospital with a 3-day history of fever, dyspnea, and productive cough of yellow sputum. Her temperature is 38.8 C (102 F), blood pressure is 110/66 mm Hg, and pulse is 110/min. She has bronchial breath sounds and crackles in the right lower lung field. Laboratory studies are as follows:

Hemoglobin	13 g/dL
Platelets	350,000/mm^3
Leukocytes	54,000/mm^3
Neutrophils	65%
Band form	10%
Myelocyte	3%
Metamyelocyte	1%
Lymphocytes	15%

The leukocyte alkaline phosphatase test score is elevated. Which of the following is the most likely additional finding on this patient's blood smear?

A. Basophilic oval inclusions in mature neutrophils
B. Basophilic stippling of red blood cells
C. Immature cells with azurophilic rods
D. Neutrophils with hypersegmented nuclei

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Platelets	350,000/mm^3
Leukocytes	54,000/mm^3
Neutrophils	65%
Band form	10%
Myelocyte	3%
Metamyelocyte	1%
Lymphocytes	15%

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A. Basophilic oval inclusions in mature neutrophils
B. Basophilic stippling of red blood cells
C. Immature cells with azurophilic rods
D. Neutrophils with hypersegmented nuclei
E. Small lymphoid cells with cleaved nuclei

Submit

Platelets	350,000/mm^3
Leukocytes	54,000/mm^3
Neutrophils	65%
Band form	10%
Myelocyte	3%
Metamyelocyte	1%
Lymphocytes	15%

The leukocyte alkaline phosphatase test score is elevated. Which of the following is the most likely additional finding on this patient's blood smear?

- A. Basophilic oval inclusions in mature neutrophils [35%]
- B. Basophilic stippling of red blood cells [4%]
- C. Immature cells with azurophilic rods [28%]
- D. Neutrophils with hypersegmented nuclei [22%]
- E. Small lymphoid cells with cleaved nuclei [9%]

Omitted
Correct answer

35%
Answered correctly

6 Seconds
Time Spent

12/12/2018
Last Updated

Settings

Item 30 of 40
Question Id: 11456

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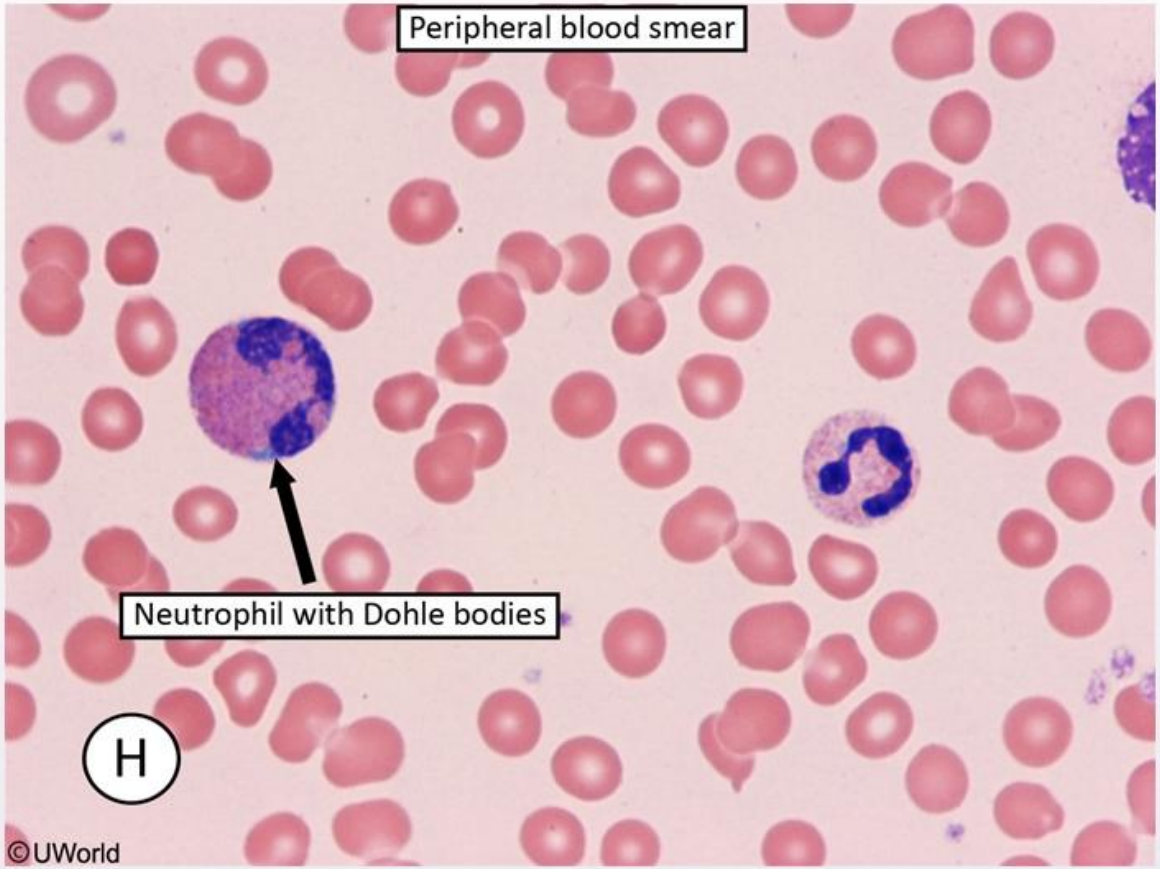

This patient most likely has pneumonia with sepsis and a **leukemoid reaction**, defined as a benign leukocytosis (>50,000/mm^3) that occurs in

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This patient most likely has pneumonia with sepsis and a **leukemoid reaction**, defined as a benign leukocytosis (>50,000/mm^3) that occurs in response to an underlying condition such as severe infection/hemorrhage, solid tumors, or acute hemolysis. The bone marrow can be normal or hypercellular and responds with increased bands and early mature neutrophil precursors (eg, myelocytes), in contrast to the increased immature cells (eg, promyelocytes, myeloblasts) seen in acute leukemia.

Serum **leukocyte alkaline phosphatase** can be normal or increased in leukemoid reaction, but it is usually low in chronic myelogenous leukemia. The peripheral smear can show **Döhle bodies**, which are light blue (**basophilic**) peripheral granules in neutrophils. The blue color is likely due to ribosomes bound with rough endoplasmic reticulum. Döhle bodies are commonly seen in toxic systemic illness but can also occur with burns or myelodysplasia. Other findings of systemic inflammation or infection include increased bands (left shift), **toxic granulation**, and **cytoplasmic vacuoles**.

(Choice B) **Basophilic stippling** refers to various sizes of blue granules representing ribosomal precipitates in the cytoplasm of red blood cells. It is most often seen in the thalassemias, alcohol abuse, and lead/heavy metal poisoning. This patient's acute presentation is more consistent with leukemoid reaction.

(Choice C) **Auer rods** are azurophilic rod-like granules in the cytoplasm of immature cells (blasts) and are essentially pathognomonic of acute myeloid leukemia. However, this patient's complete blood count shows mainly mature neutrophil precursors.

(Choice D) Neutrophils typically have nuclei with 3-4 lobes, and **hypersegmented neutrophils** with >5 lobes suggest a megaloblastic process (eg, vitamin B_{12} or folate deficiency). This patient's normal hemoglobin makes this unlikely.

(Choice E) Small lymphoid cells with increased nuclei to cytoplasmic ratio and cleaved nuclei are seen in certain types of lymphoma, particularly **follicular lymphoma**. This patient's acute presentation is more consistent with leukemoid reaction.

Educational objective:
Leukemoid reaction is a benign leukocytosis (>50,000/mm^3) that occurs in response to an underlying condition such as severe

leukemia. The peripheral smear can show **Döhle bodies**, which are light blue (**basophilic**) peripheral granules in neutrophils. The blue color is likely due to ribosomes bound with rough endoplasmic reticulum. Döhle bodies are commonly seen in toxic systemic illness but can also occur with burns or myelodysplasia. Other findings of systemic inflammation or infection include increased bands (left shift), **toxic granulation**, and **cytoplasmic vacuoles**.

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(Choice E) Small lymphoid cells with increased nuclei to cytoplasmic ratio and cleaved nuclei are seen in certain types of lymphoma, particularly **follicular lymphoma**. This patient's acute presentation is more consistent with leukemoid reaction.

Educational objective:
Leukemoid reaction is a benign leukocytosis (>50,000/mm^3) that occurs in response to an underlying condition such as severe infection/hemorrhage, malignancy (eg, leukemia), or acute hemolysis. Leukocyte alkaline phosphatase levels are normal or increased. Peripheral smear can show increased bands, early mature neutrophil precursors (eg, myelocytes), and granules (eg, Döhle bodies) in the neutrophils.

References

- An update on the etiology and diagnostic evaluation of a leukemoid reaction.

Settings

Item 30 of 40
Question Id: 11456

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

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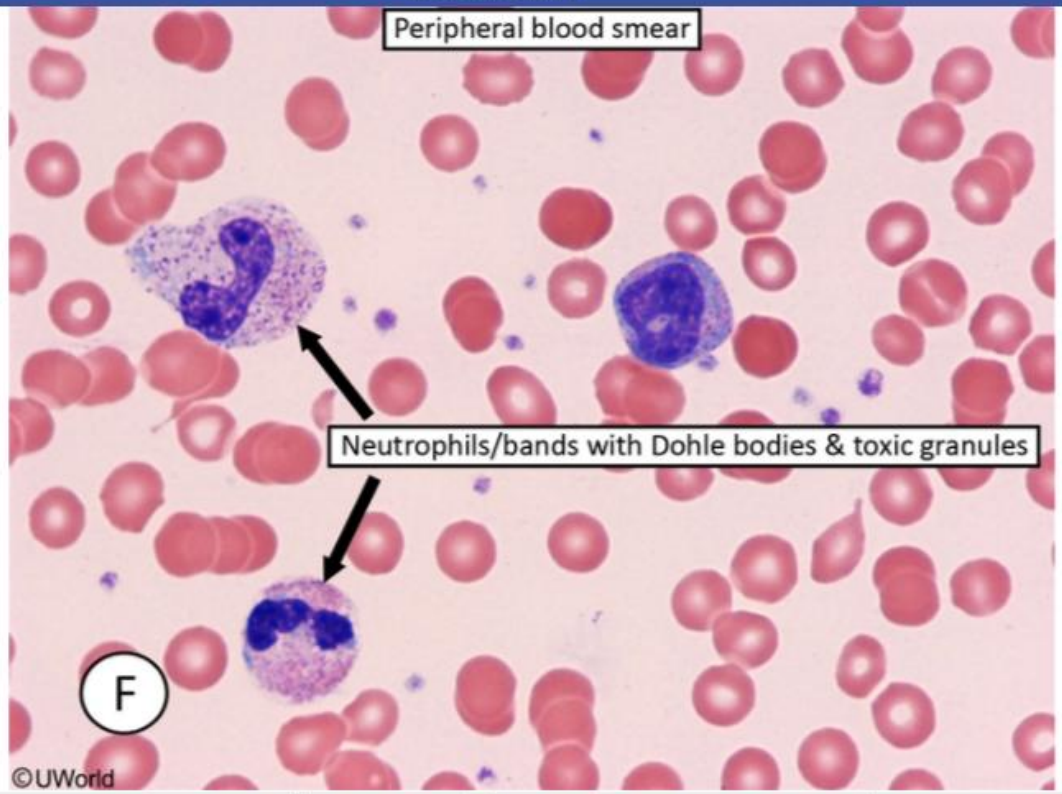

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leukemoid reaction.

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Settings

Item 30 of 40
Question Id: 11456

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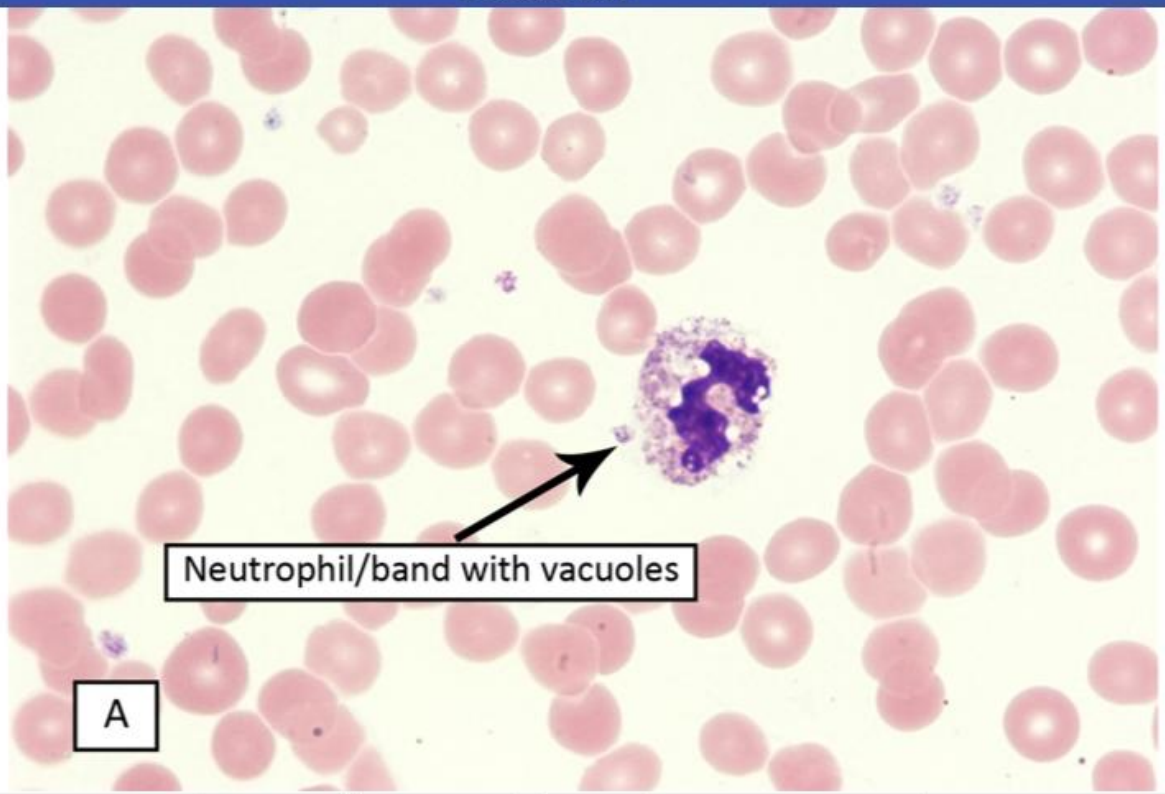

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leukemoid reaction.

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Settings

Item 31 of 40
Question Id: 1872

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

A 68-year-old man comes to the office due to an enlarging mole on his right forearm. The patient is a retired farmer and received a significant amount of sun exposure over the course of his life. On examination, he has a black-brown macular lesion on the dorsum of his right forearm measuring approximately 1 cm in diameter with an irregular border. Excisional biopsy is performed and histopathology reveals malignant melanoma. Immunohistochemical analysis indicates that the malignant cells have decreased integrin expression. These cells are most likely to exhibit poor adhesion to which of the following components of the extracellular matrix?

- A. Actin
- B. Fibronectin
- C. Hyaluronic acid
- D. Keratan sulfate
- E. Keratin

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Settings

Item 31 of 40
Question Id: 1872

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- A. Actin [12%]
- ✔ B. Fibronectin [48%]
- C. Hyaluronic acid [13%]
- D. Keratan sulfate [9%]
- E. Keratin [15%]

Omitted
Correct answer
B

48%
Answered correctly

3 Seconds
Time Spent

08/18/2018
Last Updated

Explanation

Integrin and fibronectin

Block Time Remaining: 00:03:10
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Settings

Item 31 of 40
Question Id: 1872

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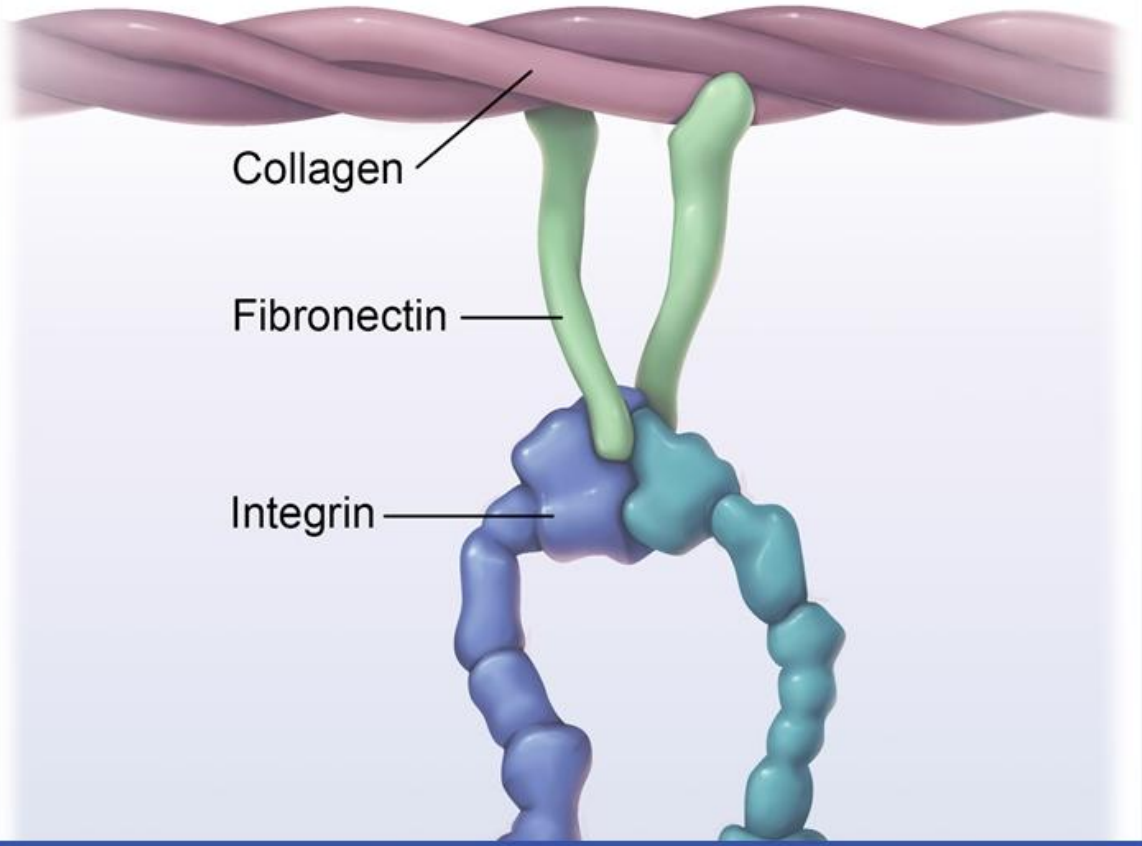
Integrin and fibronectin



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Item 31 of 40
Question Id: 1872

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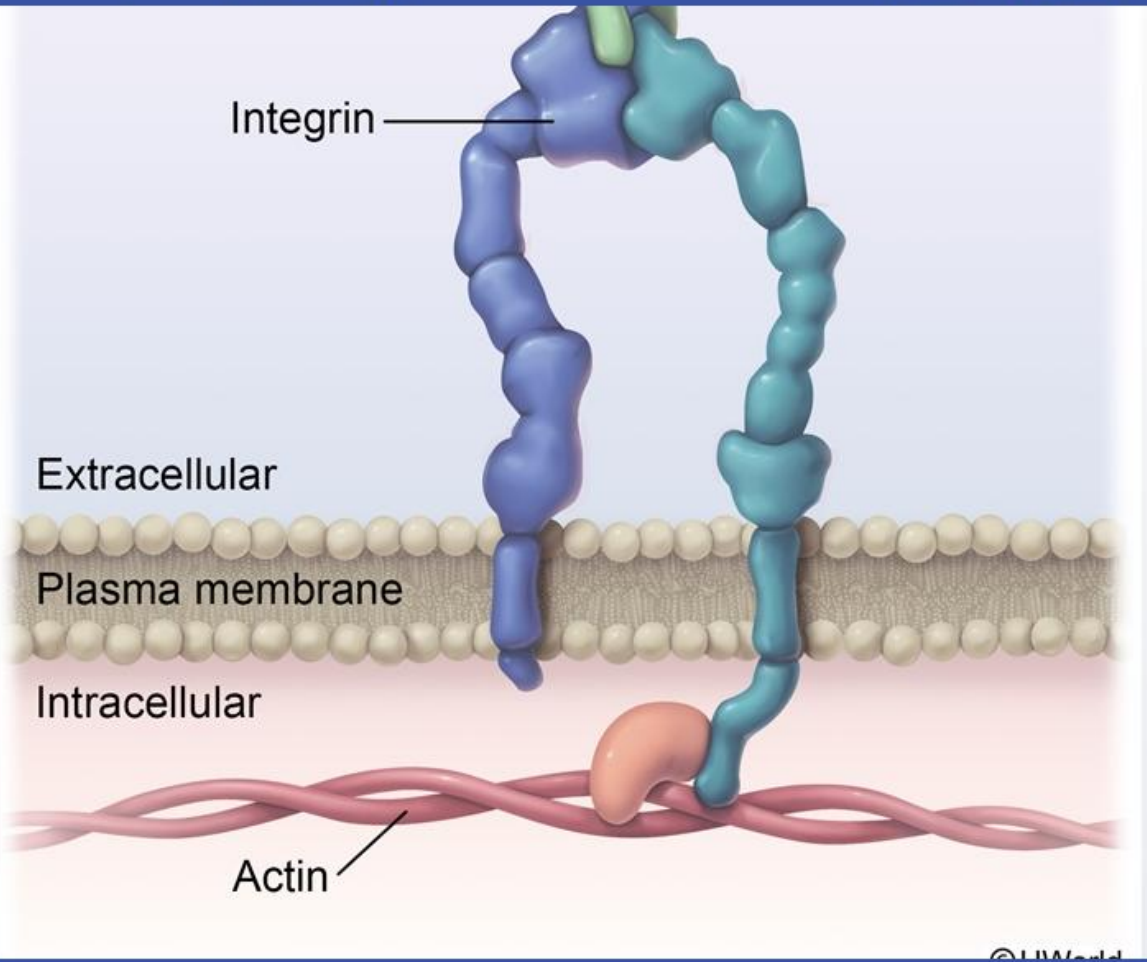

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Item 31 of 40
Question Id: 1872

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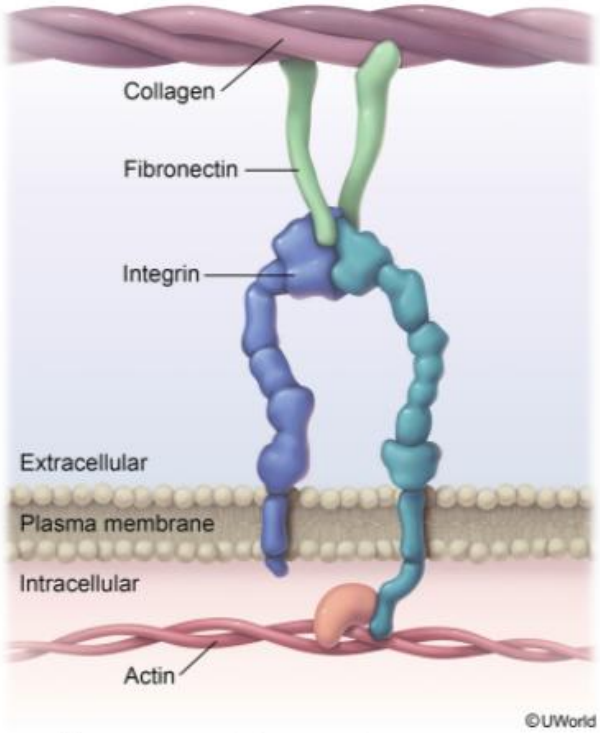
Exhibit Display

Integrin and fibronectin



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Cellular adhesion is the means by which one cell binds to another cell, surface, or matrix. The **integrins** are a family of transmembrane protein receptors that interact with the extracellular matrix by binding to specific proteins, including collagen, fibronectin, and laminin. Other adhesion molecule classes include the cadherins, selectins, and Ig superfamily members.

Fibronectins are large glycoproteins produced by fibroblasts and some epithelial cells. Fibronectin binds to integrins, matrix collagen, and glycosaminoglycans, serving as a mediator of cell adhesion and migration. Differential expression of integrin subtypes affects adhesion properties of individual cells, and correlates with **malignant behavior** in a number of tumors, including melanoma.

(Choices A and E) The intracellular domains of the integrins interact with a number of structural proteins, including microfilaments (actin) within the cytoplasm and intermediate filaments (keratin). However, the extracellular domains do not interact with these structures.

(Choices C and D) Hyaluronic acid is a glycosaminoglycan that contributes to water retention in the extracellular matrix, and determines the stiffness of the matrix. Keratan sulfate is a glycosaminoglycan in the extracellular matrix that may play a role in maintaining type I collagen fibril organization in a number of tissues (eg, cornea). However, neither of these is a ligand for integrins.

Educational objective:
Adhesion of cells to the extracellular matrix involves integrin-mediated binding to fibronectin, collagen, and laminin. Differential expression of integrin subtypes affects adhesion properties of individual cells, and has been found to correlate with malignant behavior in a number of tumors.

References

- Integrins: versatile receptors controlling melanocyte adhesion, migration, and proliferation.

Settings

Item 32 of 40
Question Id: 8540

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

A 67-year-old man comes to the office due to severe fatigue for the past several months. The patient cannot eat as much as he used to and has lost nearly 10 kg (22 lb) in the past 6 months. Physical examination shows mucosal pallor, hepatomegaly, and massive splenomegaly. Further evaluation reveals a gain-of-function mutation of a non-receptor tyrosine kinase protein in hematopoietic cells, leading to persistent activation of signal transducers and activators of transcription (STAT) proteins. This patient is most likely suffering from which of the following disorders?

- A. Acute promyelocytic leukemia
- B. Chronic lymphocytic leukemia
- C. High-grade non-Hodgkin lymphoma
- D. Mantle cell lymphoma
- E. Primary myelofibrosis

Submit

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Block Time Remaining: 00:03:11
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2/10/2019

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- A. Acute promyelocytic leukemia [16%]
- B. Chronic lymphocytic leukemia [27%]
- C. High-grade non-Hodgkin lymphoma [8%]
- D. Mantle cell lymphoma [8%]
- ✔ E. Primary myelofibrosis [39%]

Omitted
Correct answer
E

39%
Answered correctly

3 Seconds
Time Spent

02/08/2019
Last Updated

Explanation

Chronic myeloproliferative disorders		
Disorder	Diagnostic features	Mutation

Chronic myeloproliferative disorders		
Disorder	**Diagnostic features**	**Mutation**
Chronic myelogenous leukemia	Constitutional symptoms (eg, fatigue, weight loss, excessive sweating), splenomegaly & **leukocytosis with marked left shift** (eg, myelocytes, metamyelocytes, band forms)	Philadelphia chromosome t(9:22) BCR-ABL fusion protein
Essential thrombocytosis	Hemorrhagic & thrombotic symptoms (eg, easy bruising, microangiopathic occlusion), **thrombocytosis** & megakaryocytic hyperplasia	JAK2
Polycythemia vera	Pruritus, erythromelalgia, splenomegaly, thrombotic complications, **erythrocytosis** & thrombocytosis	
Primary myelofibrosis	Severe fatigue, splenomegaly (often causing early satiety/abdominal discomfort), hepatomegaly, anemia & **bone marrow fibrosis**	

The chronic myeloproliferative disorders are bone marrow diseases characterized by overproduction of myeloid cells. **Primary myelofibrosis** is

The chronic myeloproliferative disorders are bone marrow diseases characterized by overproduction of myeloid cells. **Primary myelofibrosis** is caused by atypical megakaryocytic hyperplasia, which stimulates fibroblast proliferation, resulting in progressive replacement of the marrow space by extensive collagen deposition. In the early stages, there is marrow hypercellularity with minimal fibrosis, but as the disease progresses, **pancytopenia** can result. **Hepatomegaly** and massive **splenomegaly** develop because the loss of bone marrow hematopoiesis is compensated for by extramedullary hematopoiesis. The peripheral smear characteristically shows **teardrop**-shaped red blood cells (dacrocytes) and nucleated red blood cells.

With the exception of chronic myelogenous leukemia, the chronic myeloproliferative disorders (especially polycythemia vera) frequently harbor a mutation in the nonreceptor cytoplasmic tyrosine kinase, **Janus kinase 2 (JAK2)**. This mutation results in **constitutive tyrosine phosphorylation activity**, and consequently, in the cytokine-independent activation of the signal transducers and activators of transcription **(STAT)** pathway. Once they are activated, STAT proteins translocate to the nucleus and promote transcription. A JAK2 inhibitor (ruxolitinib) has been approved for treatment of primary myelofibrosis.

(Choice A) In acute promyelocytic leukemia, t(15;17) leads to the formation of a fusion gene between the promyelocytic leukemia (*PML*) and the retinoic acid receptor alpha (*RARA*) genes. The abnormal PML/RARα fusion protein blocks differentiation of myeloid precursors.

(Choice B) Chronic lymphocytic leukemia is a lymphoproliferative disorder involving B lymphocytes. The most significant laboratory finding is marked lymphocytosis, with "smudge cells" seen on peripheral blood smear. The majority of cases exhibit increased expression of the proto-oncogene *BCL2*; a similar finding occurs in follicular lymphomas.

(Choices C and D) Several high-grade non-Hodgkin lymphomas (NHLs) are associated with cytogenetic abnormalities. The t(8;14) translocation involves the c-*Myc* oncogene and is common in Burkitt lymphoma, which is associated with Epstein-Barr virus infection and classically has a "starry sky" histological appearance. Mantle cell lymphoma is a low grade NHL characterized by t(11;14), leading to cyclin D1 overexpression.

Educational objective:
The chronic myeloproliferative disorders (polycythemia vera, essential thrombocytosis, and primary myelofibrosis) often have a mutation in Janus

With the exception of chronic myelogenous leukemia, the chronic myeloproliferative disorders (especially polycythemia vera) frequently harbor a mutation in the nonreceptor cytoplasmic tyrosine kinase, **Janus kinase 2 (JAK2)**. This mutation results in **constitutive tyrosine phosphorylation activity**, and consequently, in the cytokine-independent activation of the signal transducers and activators of transcription **(STAT)** pathway. Once they are activated, STAT proteins translocate to the nucleus and promote transcription. A JAK2 inhibitor (ruxolitinib) has been approved for treatment of primary myelofibrosis.

(Choice A) In acute promyelocytic leukemia, t(15;17) leads to the formation of a fusion gene between the promyelocytic leukemia (*PML*) and the retinoic acid receptor alpha (*RARA*) genes. The abnormal PML/RARα fusion protein blocks differentiation of myeloid precursors.

(Choice B) Chronic lymphocytic leukemia is a lymphoproliferative disorder involving B lymphocytes. The most significant laboratory finding is marked lymphocytosis, with "smudge cells" seen on peripheral blood smear. The majority of cases exhibit increased expression of the proto-oncogene *BCL2*; a similar finding occurs in follicular lymphomas.

(Choices C and D) Several high-grade non-Hodgkin lymphomas (NHLs) are associated with cytogenetic abnormalities. The t(8;14) translocation involves the c-*Myc* oncogene and is common in Burkitt lymphoma, which is associated with Epstein-Barr virus infection and classically has a "starry sky" histological appearance. Mantle cell lymphoma is a low grade NHL characterized by t(11;14), leading to cyclin D1 overexpression.

Educational objective:
The chronic myeloproliferative disorders (polycythemia vera, essential thrombocytosis, and primary myelofibrosis) often have a mutation in Janus kinase 2 (JAK2), a cytoplasmic tyrosine kinase. This results in constitutive tyrosine kinase activity, and consequently, in the cytokine-independent activation of signal transducers and activators of transcription (STAT) proteins (JAK-STAT signaling pathway).

References

- Myeloproliferative disorders.

Settings

Item 32 of 40
Question Id: 8540

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Pruritus, erythromelalgia, splenomegaly.

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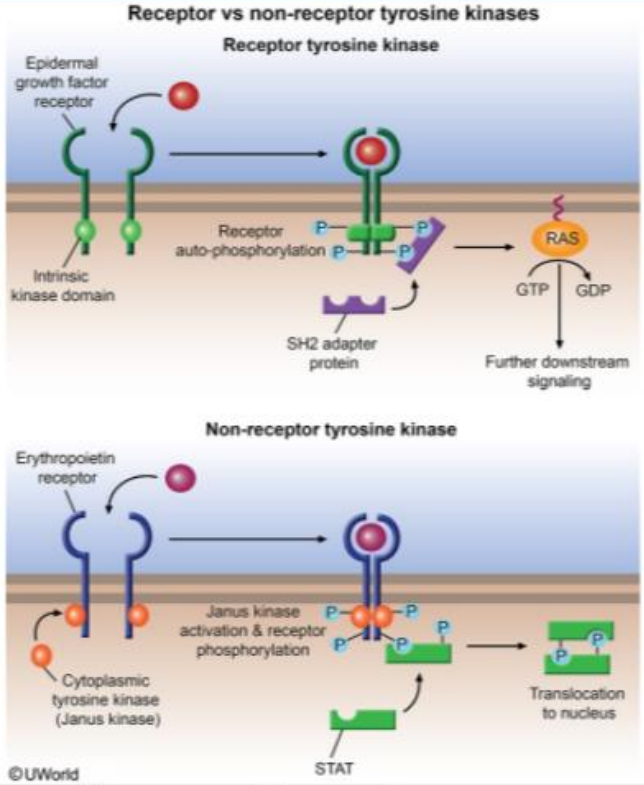

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Settings

Item 33 of 40
Question Id: 1798

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An 8-year-old boy with a one-week history of fever and throat pain is brought to the emergency department with severe dyspnea, tachypnea, and inspiratory stridor. He has also experienced worsening dysphagia with solid foods over the last two weeks. Laboratory evaluation reveals many immature hematopoietic cells (blasts) in the peripheral blood smear. The neoplastic cells causing this patient's condition normally give rise to which of the following?

- A. B-lymphocytes
- B. T-lymphocytes
- C. Monocytes
- D. Erythrocytes
- E. Platelets

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Item 33 of 40
Question Id: 1798

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An 8-year-old boy with a one-week history of fever and throat pain is brought to the emergency department with severe dyspnea, tachypnea, and inspiratory stridor. He has also experienced worsening dysphagia with solid foods over the last two weeks. Laboratory evaluation reveals many immature hematopoietic cells (blasts) in the peripheral blood smear. The neoplastic cells causing this patient's condition normally give rise to which of the following?

- A. B-lymphocytes [44%]
- ✔ B. T-lymphocytes [38%]
- C. Monocytes [8%]
- D. Erythrocytes [7%]
- E. Platelets [0%]

Omitted
Correct answer
B

38%
Answered correctly

3 Seconds
Time Spent

11/12/2018
Last Updated

Explanation

Blast cells in the peripheral blood are strongly suggestive of leukemia. The most common pediatric malignancy is acute lymphoblastic leukemia (ALL). The neoplastic cells of ALL arise from lymphocytic precursors that are of either pre-B or pre-T lineage.

Clinical manifestations of ALL include fever, fatigue, pallor, petechiae, and bleeding. Leukemic spread can cause lymphadenopathy,

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Explanation

Blast cells in the peripheral blood are strongly suggestive of leukemia. The most common pediatric malignancy is acute lymphoblastic leukemia (ALL). The neoplastic cells of ALL arise from lymphocytic precursors that are of either pre-B or pre-T lineage.

Clinical manifestations of ALL include fever, fatigue, pallor, petechiae, and bleeding. Leukemic spread can cause lymphadenopathy, hepatosplenomegaly, and bone pain. T-cell ALL is more likely to present with a large anterior mediastinal mass that can compress the great vessels, causing superior vena cava syndrome. The mediastinal mass can also compress the esophagus causing dysphagia, while compression of the trachea may lead to dyspnea and stridor. This patient's clinical presentation is therefore most suggestive of T-cell ALL, which most commonly affects males in late childhood through young adulthood.

Because pre-B and pre-T lymphoblasts can look identical on peripheral blood smear, immunohistochemical staining is used to differentiate the two cell lineages. Both lineages contain TdT (an antigen of lymphocyte precursors). Cell surface markers for pre-B lymphoblasts include CD10+, CD 19+, and CD20+; while pre-T lymphoblasts express CD2+, CD3+, CD4+, CD5+, CD7+, and CD8+.

(Choice A) B-cell ALL is responsible for approximately 70-80% of all cases of ALL, whereas T-cell ALL accounts for 15-17% of all cases of ALL. B-cell ALL manifests with fever, malaise, bleeding, bone pain, and hepatosplenomegaly. Generally, B-cell ALL is not associated with symptoms of mediastinal compression.

(Choice C) Acute myeloid leukemia (AML) subtypes M4 and M5 arise from monocytic precursors. This is rarely seen in children and usually does not present as a mediastinal mass, though extramedullary disease is not an uncommon finding.

(Choice D) The rare AML M6 subtype arises from erythroid precursors and typically affects elderly patients.

(Choice E) The rare AML M7 subtype arises from primitive megakaryoblasts and is associated with t(1;22) and Down syndrome in children.

Educational objective:
Acute lymphoblastic leukemia (ALL) is the most common malignancy of childhood. B-cell ALL is responsible for approximately 70-80% of all cases of ALL, whereas T-cell ALL accounts for 15-17% of all cases of ALL. T-cell ALL often presents as a mediastinal mass that can cause

(ALL). The neoplastic cells of ALL arise from lymphocytic precursors that are of either pre-B or pre-T lineage.

Clinical manifestations of ALL include fever, fatigue, pallor, petechiae, and bleeding. Leukemic spread can cause lymphadenopathy, hepatosplenomegaly, and bone pain. T-cell ALL is more likely to present with a large anterior mediastinal mass that can compress the great vessels, causing superior vena cava syndrome. The mediastinal mass can also compress the esophagus causing dysphagia, while compression of the trachea may lead to dyspnea and stridor. This patient's clinical presentation is therefore most suggestive of T-cell ALL, which most commonly affects males in late childhood through young adulthood.

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(Choice D) The rare AML M6 subtype arises from erythroid precursors and typically affects elderly patients.

(Choice E) The rare AML M7 subtype arises from primitive megakaryoblasts and is associated with t(1;22) and Down syndrome in children.

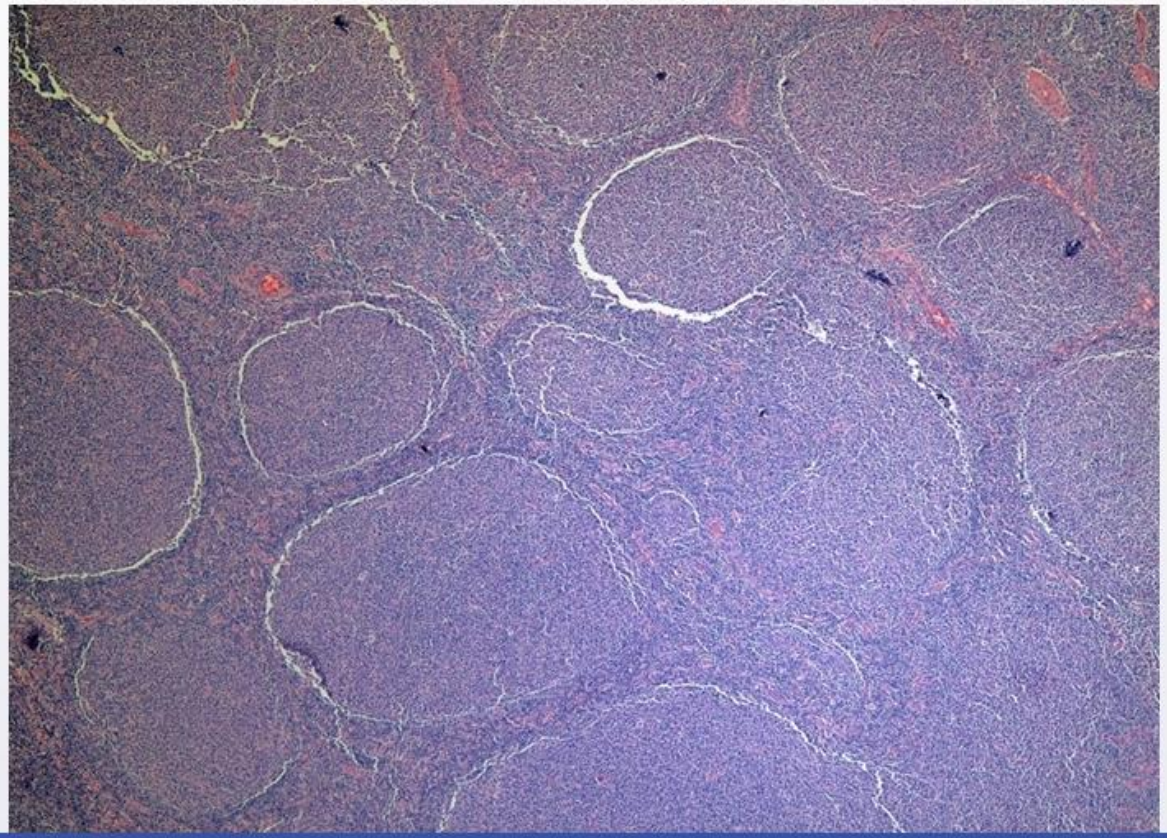
Educational objective:
Acute lymphoblastic leukemia (ALL) is the most common malignancy of childhood. B-cell ALL is responsible for approximately 70-80% of all cases of ALL, whereas T-cell ALL accounts for 15-17% of all cases of ALL. T-cell ALL often presents as a mediastinal mass that can cause respiratory symptoms, dysphagia, or superior vena cava syndrome.

Settings

Item 34 of 40
Question Id: 1627

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

A 35-year-old man is being evaluated for nontender cervical lymphadenopathy that he first noticed while shaving. A biopsy is performed, and a low-magnification image of the lymph node histology is shown below.



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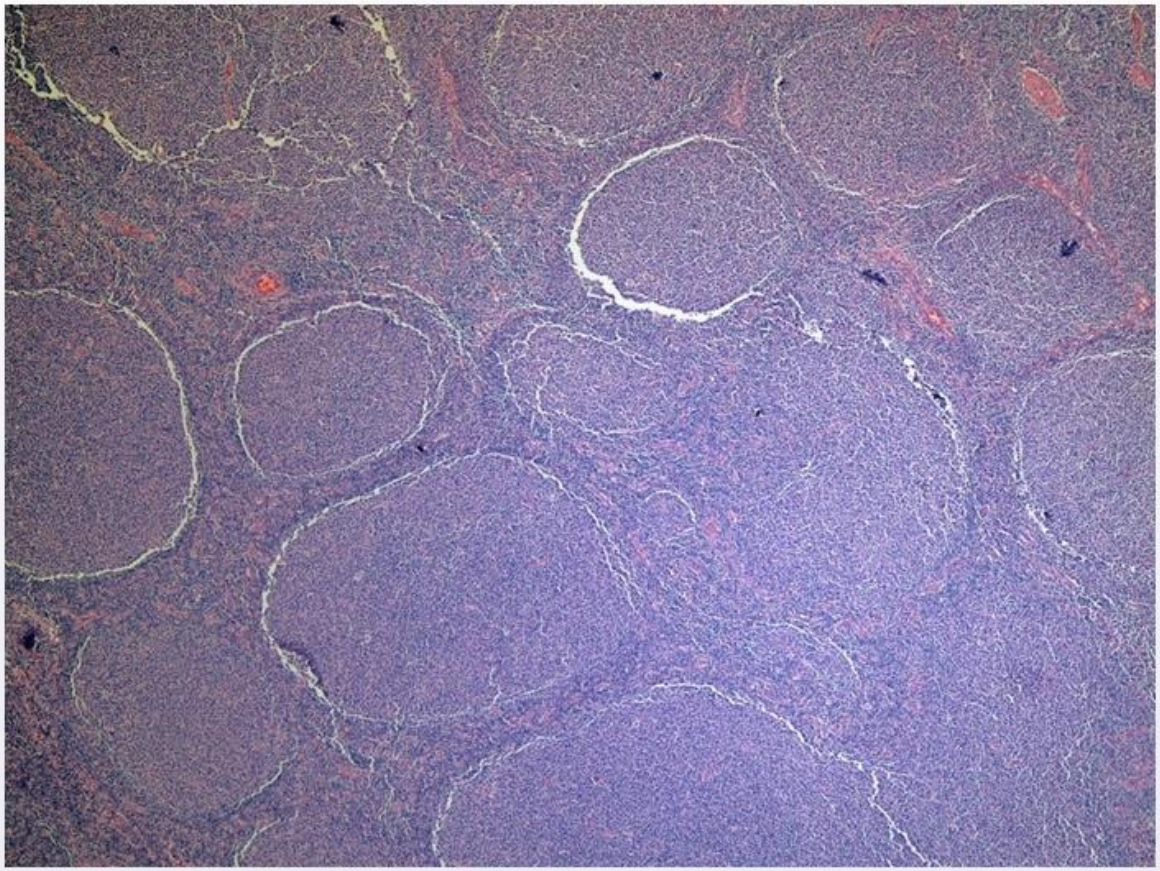
Settings

Item 34 of 40
Question Id: 1627

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

low-magnification image of the lymph node histology is shown below.



Cytogenetic analysis would most likely demonstrate which of the following patterns?

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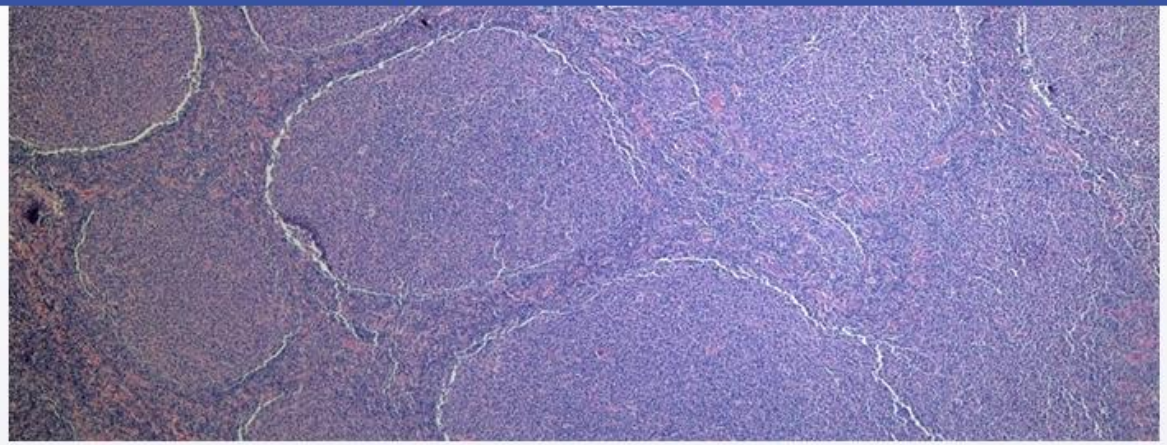
Item 34 of 40
Question Id: 1627

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



Cytogenetic analysis would most likely demonstrate which of the following patterns?

- A. BCL-2 overexpression
- B. *BCR-ABL* rearrangement
- C. C-MYC overexpression
- D. Constitutive tyrosine kinase activation
- E. N-MYC overexpression

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Settings

Item 34 of 40
Question Id: 1627

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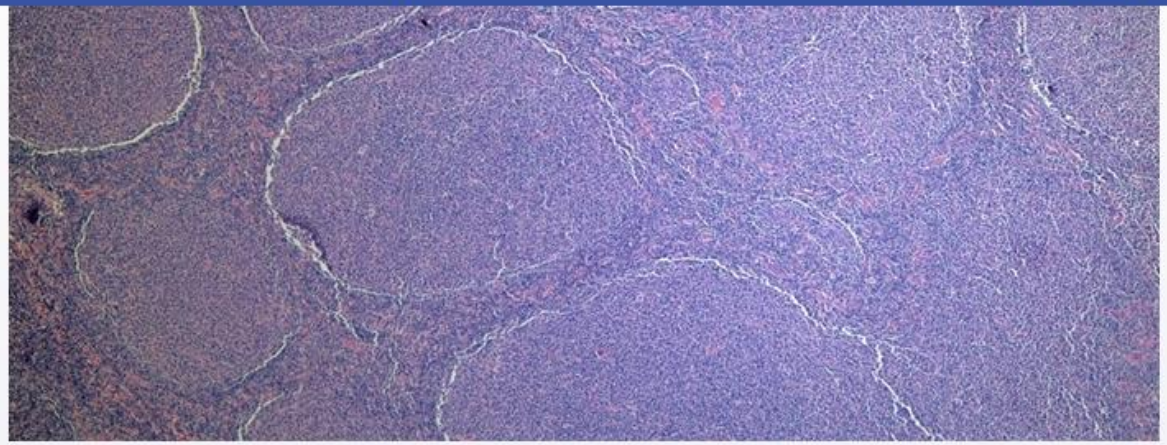

Cytogenetic analysis would most likely demonstrate which of the following patterns?

- A. BCL-2 overexpression [69%]
- B. *BCR-ABL* rearrangement [8%]
- C. C-MYC overexpression [16%]
- D. Constitutive tyrosine kinase activation [3%]
- E. N-MYC overexpression [2%]

Omitted
Correct answer

69%
Answered correctly

18 Seconds
Time Spent

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Last Updated

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Settings

Item 34 of 40
Question Id: 1627

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

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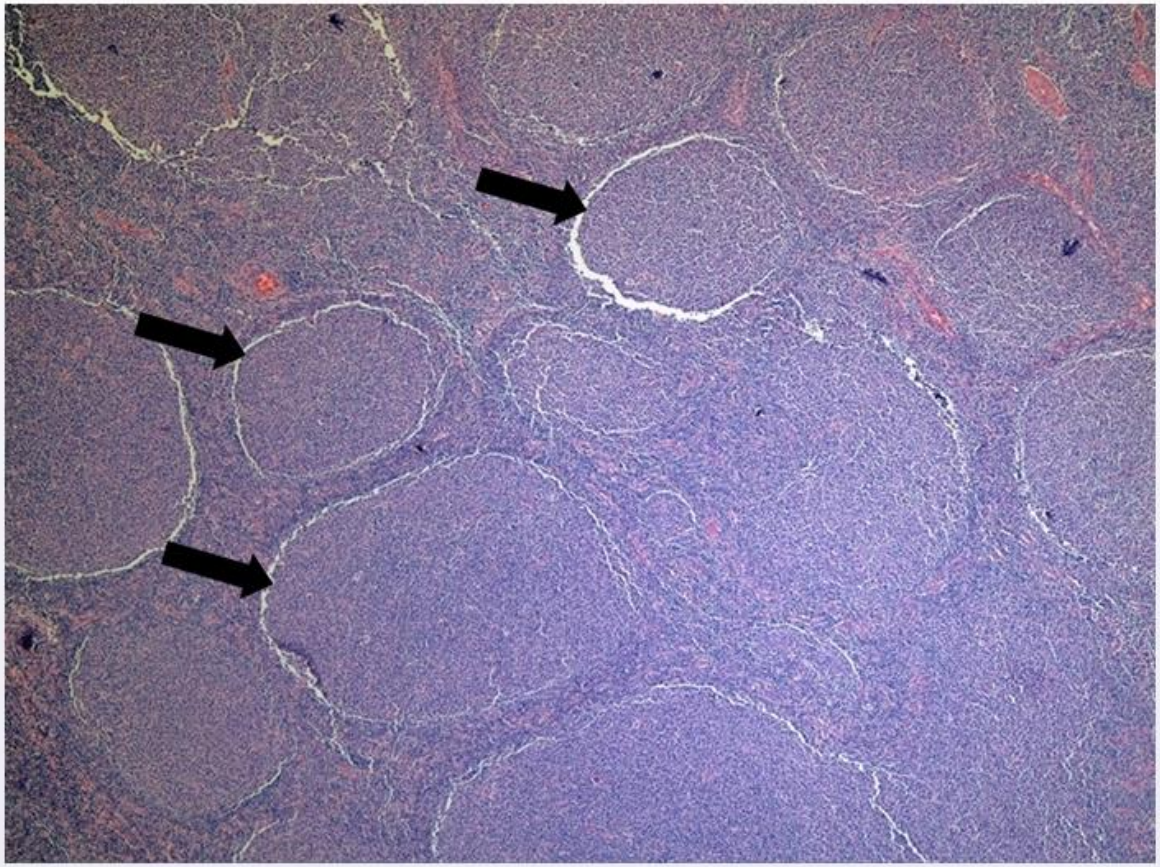
Explanation



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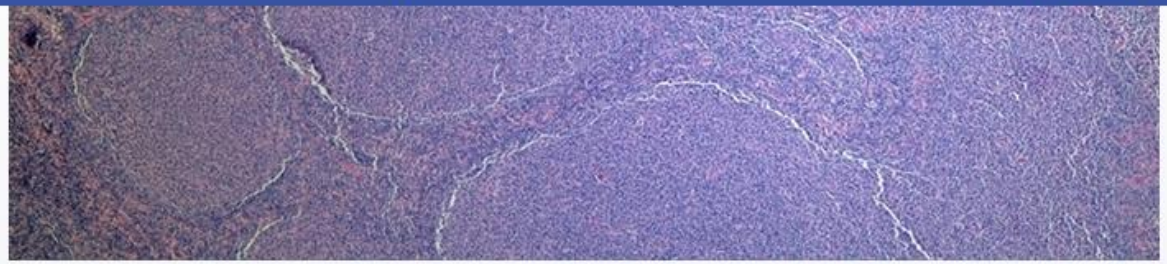

The image demonstrates the classic histology of follicular lymphoma, a type of non-Hodgkin's lymphoma. Follicular lymphoma is a B-cell tumor composed predominantly of **centrocytes** (small cleaved cells) and fewer numbers of centroblasts (large noncleaved cells). At low magnification, aggregates of packed follicles (arrows) that obscure the normal lymph node architecture are seen. The t(14;18) translocation is found in 80%-90% of follicular lymphomas. The result is overexpression of the antiapoptotic gene product, BCL-2, and tumor formation.

(Choices B and D) *BCR-ABL* rearrangement t(9;22) is found in chronic myelogenous leukemia (CML). CML is a myeloproliferative disorder, not a lymphoproliferative disorder as shown in the image above. The *BCR-ABL* fusion gene directs the synthesis of a constitutively active protein tyrosine kinase that affects multiple intracellular signaling pathways, leading to uncontrolled proliferation.

(Choice C) All Burkitt lymphomas 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)]. Histologically, **Burkitt lymphoma** shows a diffuse population of medium-sized lymphocytes with a "starry sky" appearance due to the high proliferation index and high rate of apoptosis.

(Choice E) Overexpression of N-MYC proto-oncogene protein is common in neuroblastoma and small cell carcinoma of the lung.

Educational objective:
Follicular lymphoma is characterized by aggregates of packed follicles that obscure the normal lymph node architecture. Ninety percent of patients with follicular lymphoma have the t(14;18) translocation, which causes overexpression of the antiapoptotic BCL-2 protein.

Settings

Item 34 of 40
Question Id: 1627

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

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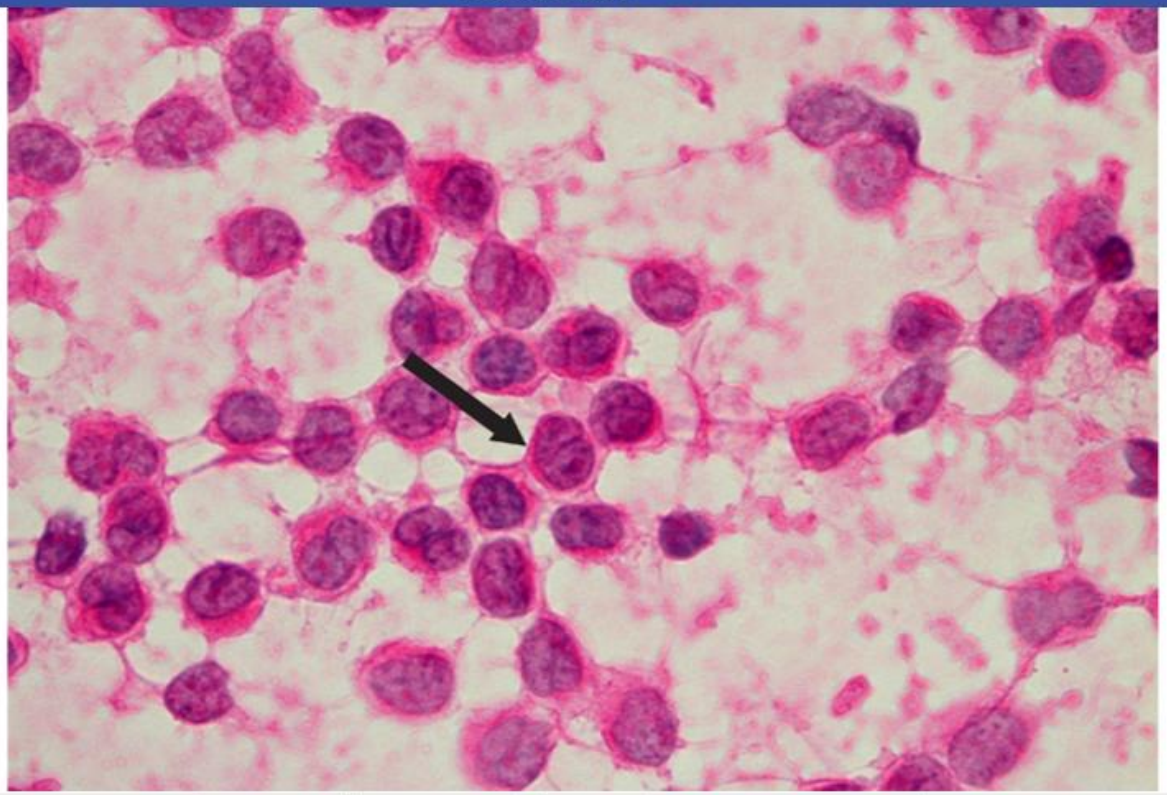

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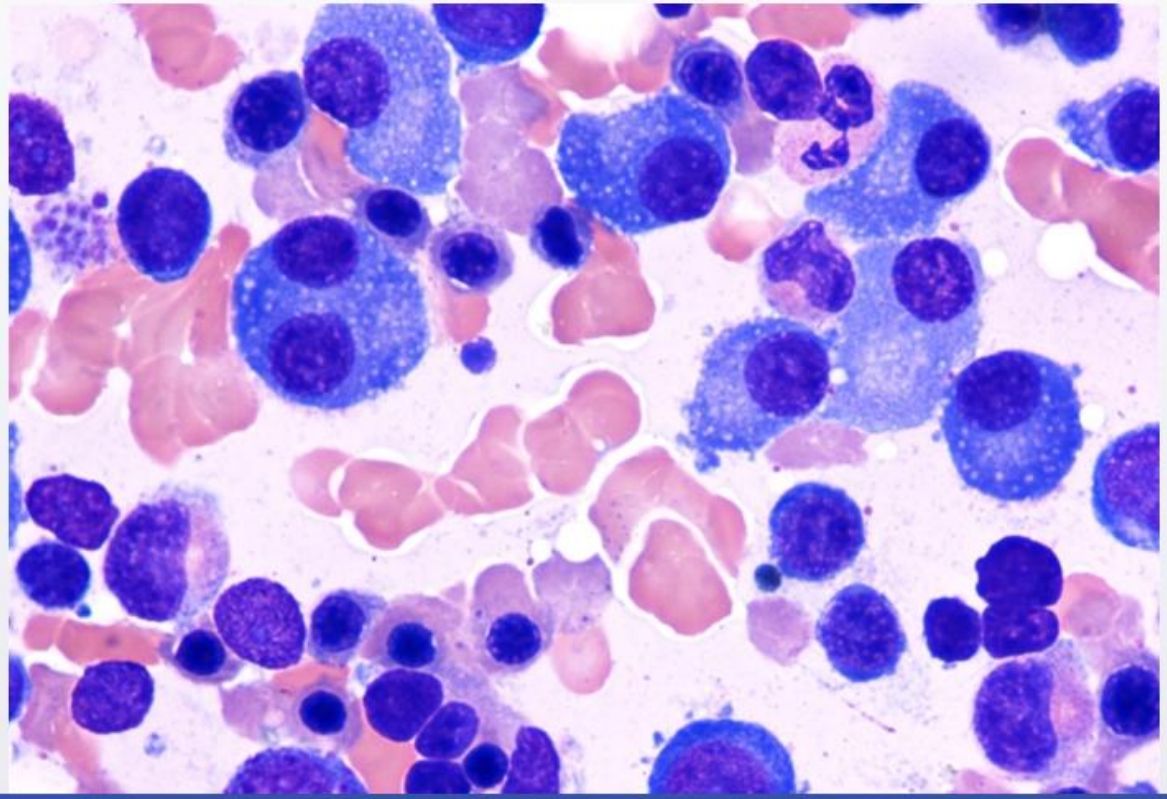
Settings

Item 35 of 40
Question Id: 872

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

A 59-year-old man comes to the office due to 3 months of progressive fatigue and back pain. The back pain occurs mainly with movement or positional changes. Physical examination reveals midline tenderness over the middle and lower back. Laboratory evaluation shows a hemoglobin level of 10.2 g/dL and serum calcium level of 12 mg/dL. A bone marrow aspirate is performed, and the histopathologic findings are shown below.



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Settings

Item 35 of 40
Question Id: 872

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

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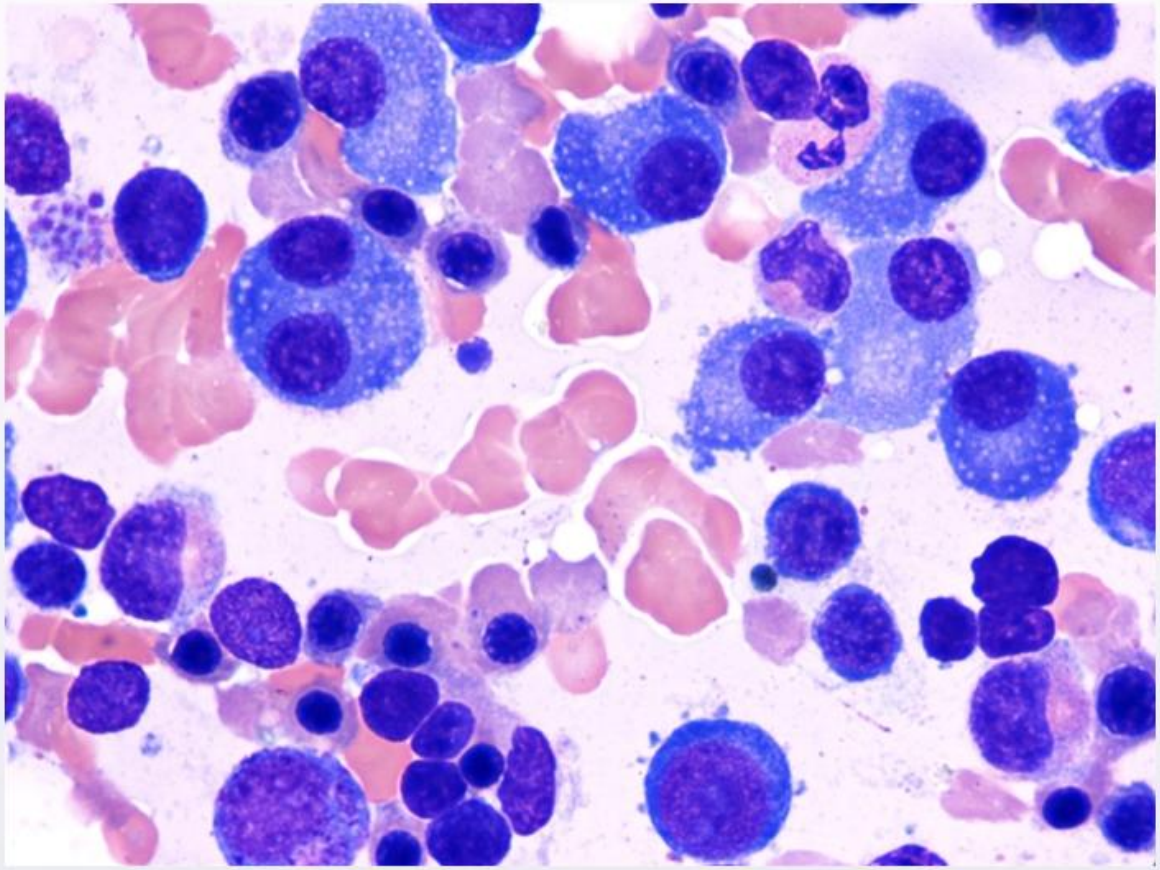

This patient is at greatest risk for which of the following?

Block Time Remaining: 00:03:41
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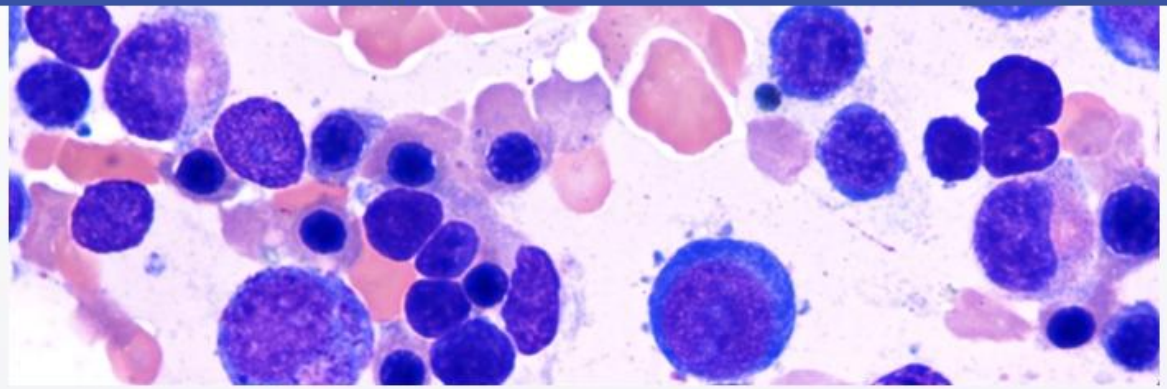
Settings

Item 35 of 40
Question Id: 872

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



This patient is at greatest risk for which of the following?

- A. Amyloidosis
- B. Cardiac tamponade
- C. Hepatic failure
- D. Hyperthyroidism
- E. Meningeal carcinomatosis
- F. Splenic rupture

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Settings

Item 35 of 40
Question Id: 872

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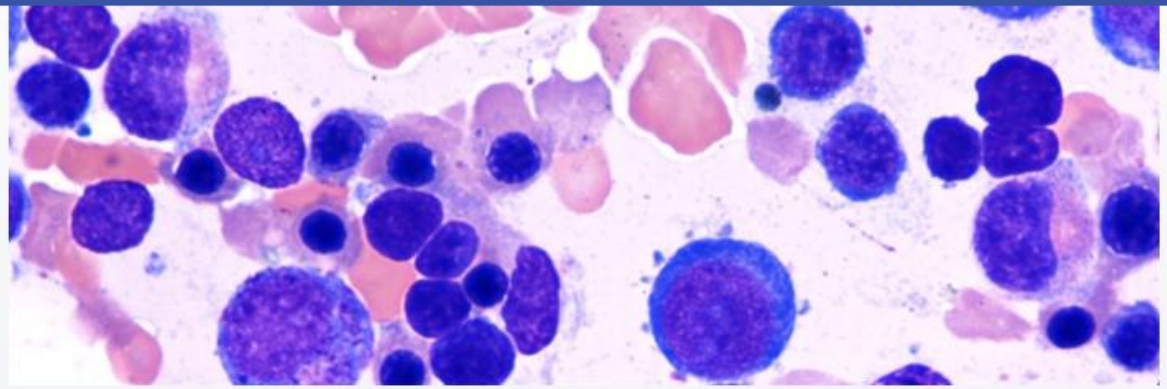

This patient is at greatest risk for which of the following?

- A. Amyloidosis [69%] ✔
- B. Cardiac tamponade [2%]
- C. Hepatic failure [5%]
- D. Hyperthyroidism [1%]
- E. Meningeal carcinomatosis [3%]
- F. Splenic rupture [17%]

Omitted
Correct answer

69%
Answered correctly

11 Seconds
Time Spent

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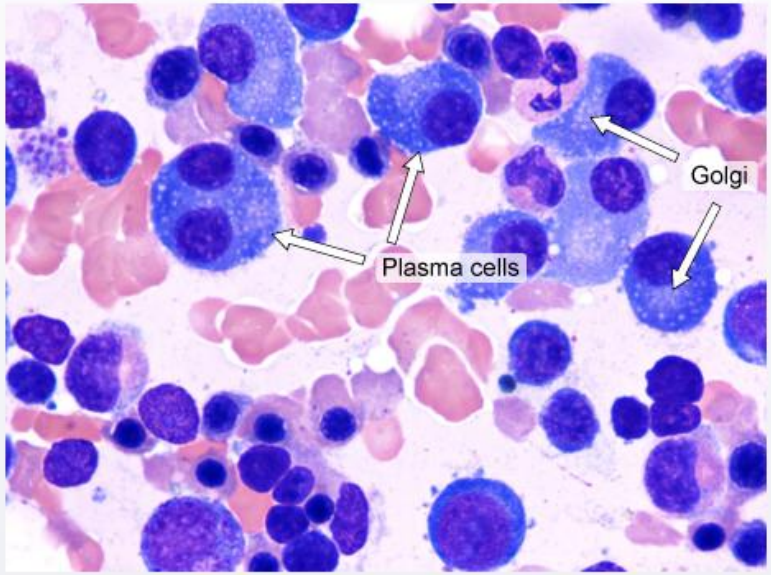
Explanation



This patient's bone marrow aspirate shows **numerous plasma cells**, which can be identified by abundant basophilic cytoplasm, well-developed Golgi apparatus (perinuclear paleness), and "clock-face" (peripheral) chromatin. A bone marrow sample with >10% plasma cells is strongly suggestive of **multiple myeloma** (MM), a clonal plasma cell malignancy.

In MM, neoplastic plasma cells:

- Replicate in the bone marrow and choke out normal hematopoiesis, leading to **normocytic**, **normochromic anemia** (impaired erythropoiesis) and increased risk of infection (impaired B-cell lymphopoiesis).
- Secrete osteolytic cytokines, leading to bone pain, osteolytic (radiolucent) bone lesions, and **hypercalcemia**

Golgi apparatus (perinuclear paleness), and "clock-face" (peripheral) chromatin. A bone marrow sample with >10% plasma cells is strongly suggestive of **multiple myeloma** (MM), a clonal plasma cell malignancy.

In MM, neoplastic plasma cells:

- Replicate in the bone marrow and choke out normal hematopoiesis, leading to **normocytic**, **normochromic anemia** (impaired erythropoiesis) and increased risk of infection (impaired B-cell lymphopoiesis).
- Secrete osteolytic cytokines, leading to bone pain, osteolytic (radiolucent) bone lesions, and **hypercalcemia**.
- Produce large quantities of **monoclonal immunoglobulin** (paraprotein) composed of heavy and light chains (eg, IgG, IgA) or light chains alone. Light chains can deposit in the renal tubules, leading to **light-chain cast nephropathy**, which is usually characterized by mild renal insufficiency and waxy, laminated urinary casts (Bence Jones).
- Light chains can also form **insoluble fibrils** and deposit in major organs, leading to **amyloid light-chain amyloidosis**. This can contribute to the already elevated risk of renal failure as well as heart failure and neurologic dysfunction. Amyloidosis can often be identified on biopsy using hematoxylin and eosin stain (eosinophilic extracellular deposits) or Congo red stain viewed under polarized light (**apple-green birefringence**).

(Choice B) Cardiac tamponade can be associated with some neoplasms (eg, lung, breast, Hodgkin disease, melanoma) due to tumor invasion of the pericardium. MM does not typically cause pericardial disease; therefore, it is not associated with cardiac tamponade.

(Choice C) Hepatic failure is most often linked to viral hepatitis or alcohol abuse. It occasionally occurs due to malignant infiltration of the liver with metastatic breast cancer, small cell lung cancer, melanoma, or lymphoma. Risk of hepatic failure with MM is low; amyloidosis is far more common.

(Choice D) Hyperthyroidism is most often due to Graves disease, an autoimmune disorder that generates TSH-receptor antibodies. It can also be seen with medications (eg, lithium) and tumors that produce TSH (eg, pituitary adenoma). MM is not linked to hyperthyroidism.

(Choice E) Meningeal carcinomatosis is a rare condition associated with some solid tumors (eg, breast cancer, lung cancer, melanoma). Tumor spread to the leptomeninges can cause mass effect (eg, headache, hydrocephalus), cranial/spinal nerve dysfunction, and focal neurologic issues

to the already elevated risk of renal failure as well as heart failure and neurologic dysfunction. Amyloidosis can often be identified on biopsy using hematoxylin and eosin stain (eosinophilic extracellular deposits) or Congo red stain viewed under polarized light (**apple-green birefringence**).

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(Choice C) Hepatic failure is most often linked to viral hepatitis or alcohol abuse. It occasionally occurs due to malignant infiltration of the liver with metastatic breast cancer, small cell lung cancer, melanoma, or lymphoma. Risk of hepatic failure with MM is low; amyloidosis is far more common.

(Choice D) Hyperthyroidism is most often due to Graves disease, an autoimmune disorder that generates TSH-receptor antibodies. It can also be seen with medications (eg, lithium) and tumors that produce TSH (eg, pituitary adenoma). MM is not linked to hyperthyroidism.

(Choice E) Meningeal carcinomatosis is a rare condition associated with some solid tumors (eg, breast cancer, lung cancer, melanoma). Tumor spread to the leptomeninges can cause mass effect (eg, headache, hydrocephalus), cranial/spinal nerve dysfunction, and focal neurologic issues. MM does not typically spread to the leptomeninges.

(Choice F) Atraumatic splenic rupture can occur with leukemia and lymphoma due to massive splenomegaly from extramedullary hematopoiesis and/or underlying tumor infiltration. MM does not typically cause significant extramedullary hematopoiesis and usually replicates in the bone marrow, not the spleen.

Educational objective:
Amyloid light-chain amyloidosis is associated with multiple myeloma and other monoclonal plasma cell dyscrasias due to the deposition of insoluble immunoglobulin light-chain fibrils in major organs (eg, kidneys, heart, neurologic system). A bone marrow sample with >10% plasma cells is strongly suggestive of multiple myeloma.

References

Settings

Item 35 of 40
Question Id: 872

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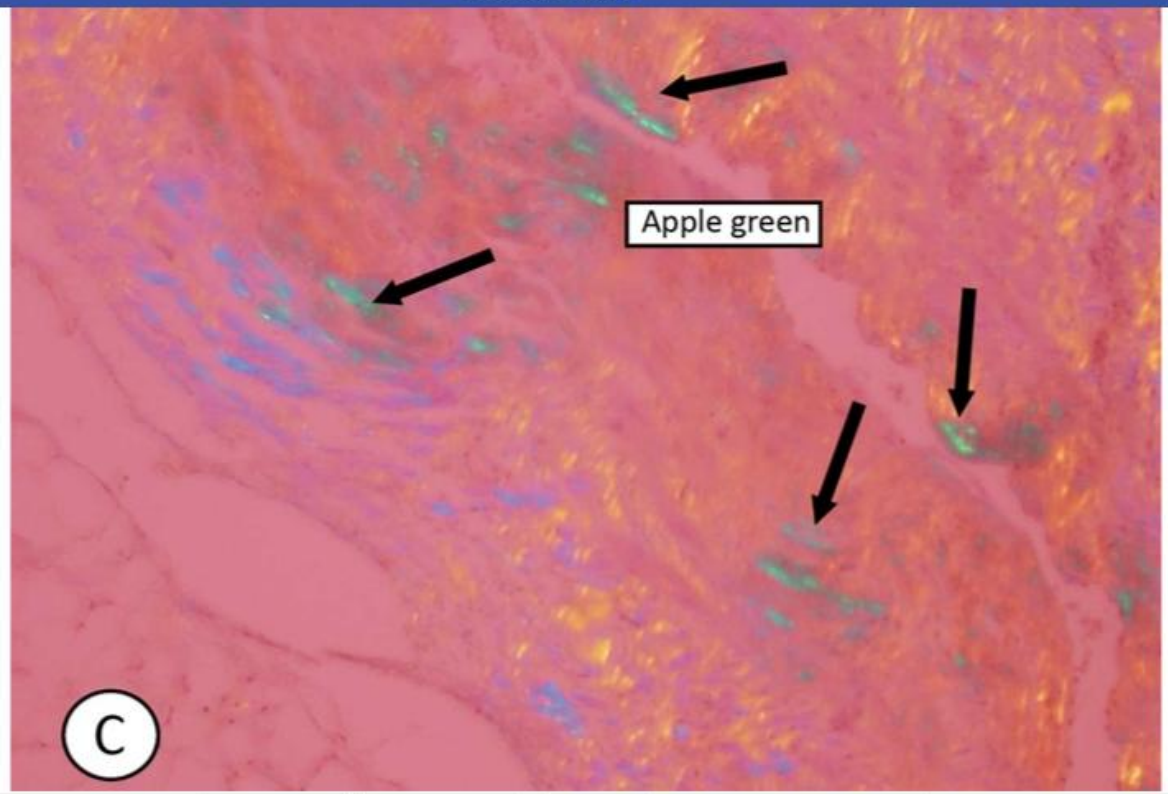

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(Choice D) Hyperthyroidism is most often due to Graves disease, an autoimmune disorder that generates TSH-receptor antibodies. It can also

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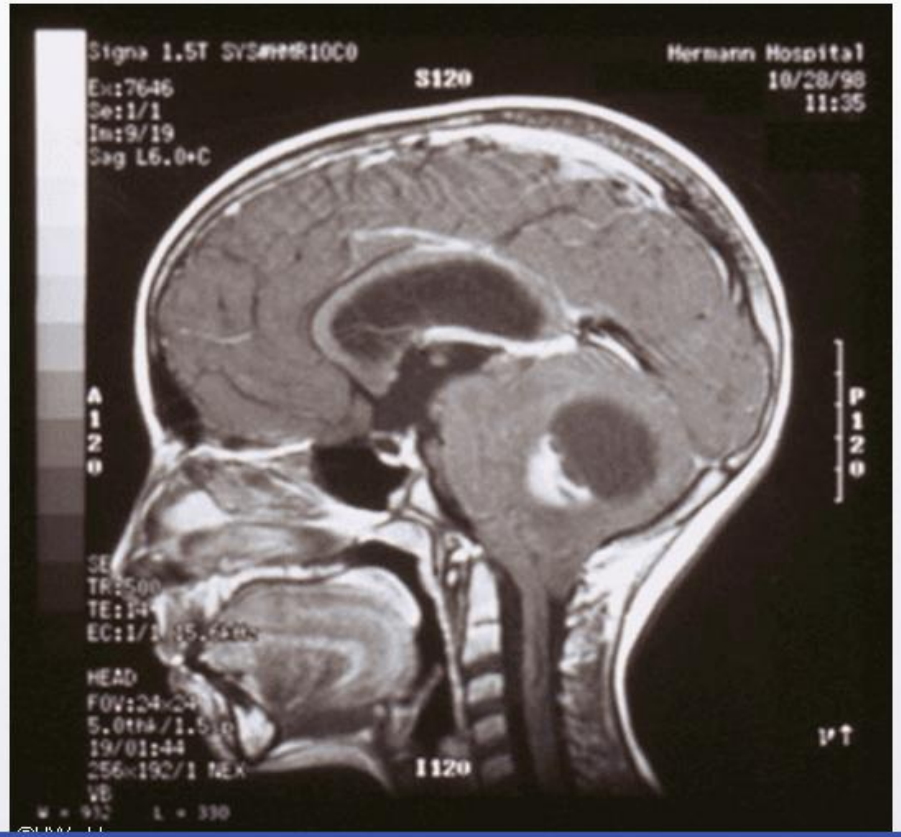
Settings

Item 36 of 40
Question Id: 615

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

A 12-year-old boy is brought to the office by his mother due to headaches and gait instability. His symptoms began several months ago and have progressively worsened. MRI of the brain is shown in the image below.



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Item 36 of 40
Question Id: 615

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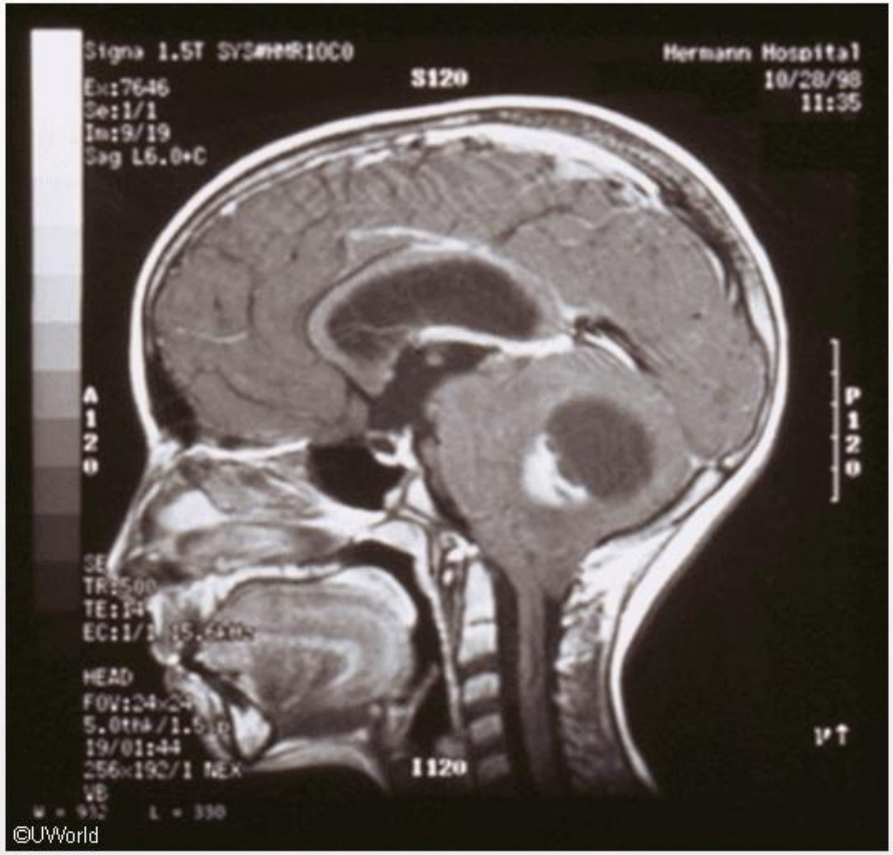

Which of the following is the most likely diagnosis?

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Item 36 of 40
Question Id: 615

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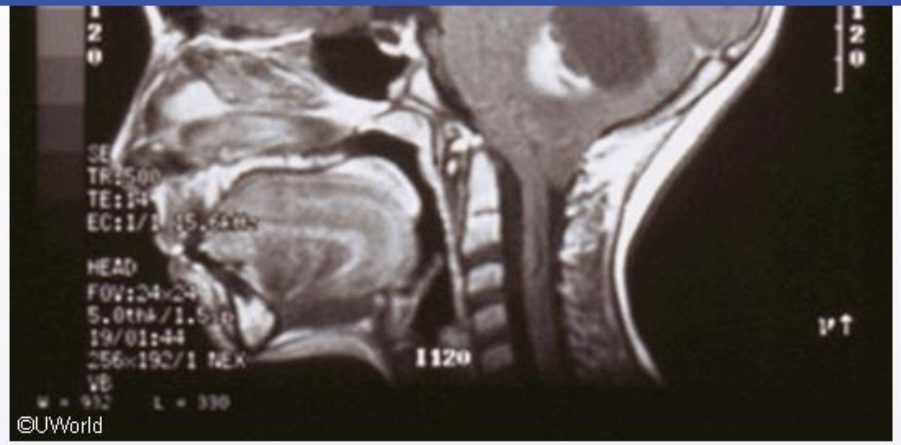

Which of the following is the most likely diagnosis?

A. Ependymoma
B. Glioblastoma multiforme
C. Medulloblastoma
D. Oligodendroglioma
E. Pilocytic astrocytoma

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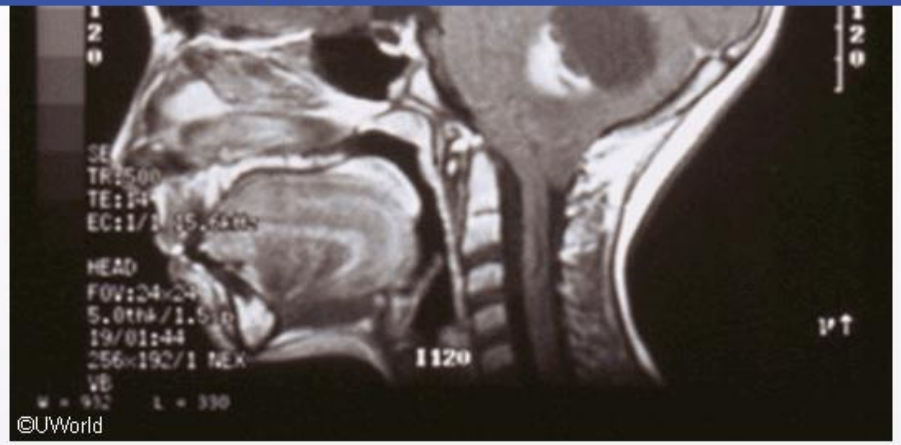
Item 36 of 40
Question Id: 615

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



Which of the following is the most likely diagnosis?

- A. Ependymoma [9%]
- B. Glioblastoma multiforme [4%]
- C. Medulloblastoma [38%]
- D. Oligodendroglioma [1%]
- ✔ E. Pilocytic astrocytoma [46%]

Omitted
Correct answer

46%
Answered correctly

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Time Spent

12/07/2018
Last Updated

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Settings

Item 36 of 40
Question Id: 615

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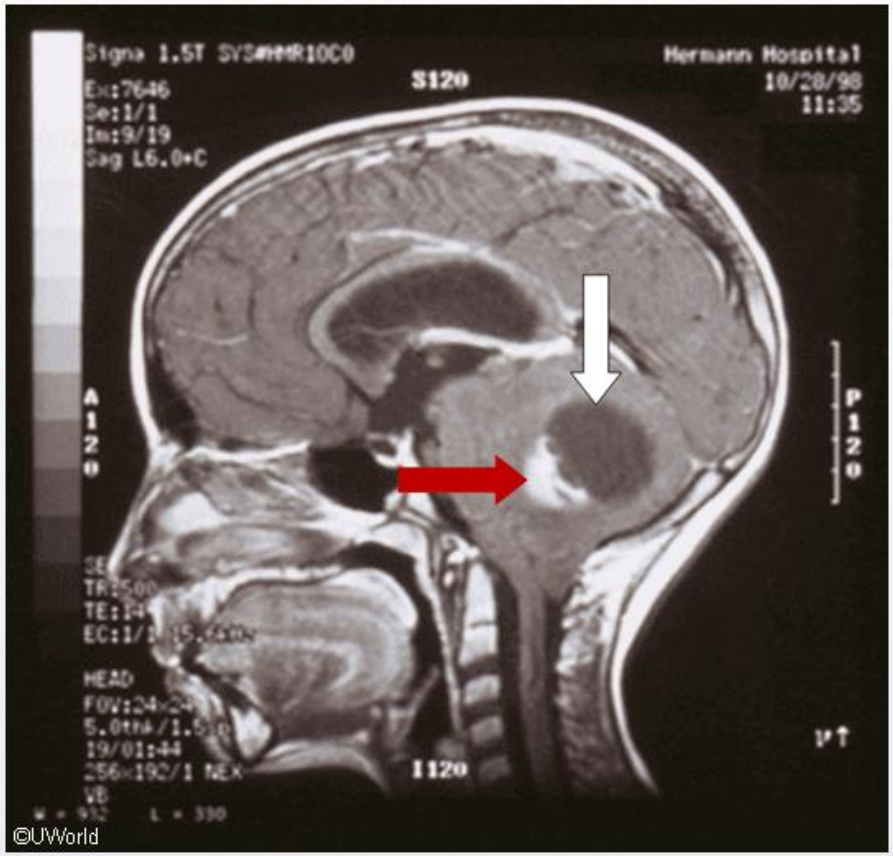

Brain tumors are the second most common childhood cancer (after leukemia) and the most common solid organ tumors of childhood. This child

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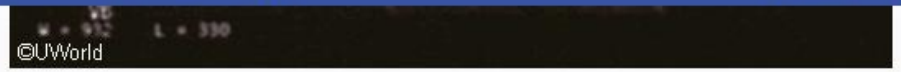

Brain tumors are the second most common childhood cancer (after leukemia) and the most common solid organ tumors of childhood. This child with a heterogeneous, well-circumscribed cerebellar mass most likely has a **pilocytic astrocytoma**, the most common type of brain tumor in children.

Pilocytic astrocytomas are **low-grade** gliomas that occur most frequently in the **cerebellum**. Patients typically have headaches and cerebellar findings (eg, loss of balance, incoordination). Imaging (shown above) reveals a well-demarcated lesion comprised of **cystic and solid components** (white and red arrows, respectively). Microscopic examination shows pilocytic astrocytes with bundles of **glial fibrillary acidic protein (GFAP)-positive hairlike processes** and classic **Rosenthal fibers** (eosinophilic intracytoplasmic inclusions). Due to the slow-growing (benign) nature, the majority of patients can be treated with surgical resection and have a favorable prognosis.

(Choice A) Ependymomas are rare tumors arising from the ependymal lining of the ventricle. They commonly occupy the 4th ventricle and can cause hydrocephalus by obstructing the flow of cerebrospinal fluid. **Perivascular pseudorosettes** are present on microscopy.

(Choice B) Glioblastoma multiforme, a tumor arising from GFAP-positive astrocytes, occurs most frequently in adults and is typically located within the cerebral hemispheres (often crossing the corpus callosum). **Pseudopalisading** pleomorphic cells with areas of necrosis are seen on microscopy.

(Choice C) Medulloblastoma is the most common *malignant* childhood brain cancer. It is located exclusively in the cerebellum; however, it is not cystic like pilocytic astrocytoma. Imaging reveals a **solid lesion** (encircled) that can compress the 4th ventricle, causing hydrocephalus (arrow). It is composed of small cells with hyperchromatic nuclei that form Homer Wright rosettes (groupings of cells surrounding the neuropil).

(Choice D) Oligodendrogliomas, rare in children, are frequently **calcified**, well-circumscribed masses located in the frontal lobe. Microscopy shows uniform cells with a **"fried egg" appearance** (ie, round nuclei with clear cytoplasm) surrounded by anastomosing capillaries arranged in a "chicken-wire" pattern.

Educational objective:

Pilocytic astrocytomas are the most common brain tumors in children. They frequently arise in the cerebellum and can be differentiated from

(Choice A) Ependymomas are rare tumors arising from the ependymal lining of the ventricle. They commonly occupy the 4th ventricle and can cause hydrocephalus by obstructing the flow of cerebrospinal fluid. **Perivascular pseudorosettes** are present on microscopy.

(Choice B) Glioblastoma multiforme, a tumor arising from GFAP-positive astrocytes, occurs most frequently in adults and is typically located within the cerebral hemispheres (often crossing the corpus callosum). **Pseudopalisading** pleomorphic cells with areas of necrosis are seen on microscopy.

(Choice C) Medulloblastoma is the most common *malignant* childhood brain cancer. It is located exclusively in the cerebellum; however, it is not cystic like pilocytic astrocytoma. Imaging reveals a **solid lesion** (encircled) that can compress the 4th ventricle, causing hydrocephalus (arrow). It is composed of small cells with hyperchromatic nuclei that form Homer Wright rosettes (groupings of cells surrounding the neuropil).

(Choice D) Oligodendrogliomas, rare in children, are frequently **calcified**, well-circumscribed masses located in the frontal lobe. Microscopy shows uniform cells with a **"fried egg" appearance** (ie, round nuclei with clear cytoplasm) surrounded by anastomosing capillaries arranged in a "chicken-wire" pattern.

Educational objective:
Pilocytic astrocytomas are the most common brain tumors in children. They frequently arise in the cerebellum and can be differentiated from medulloblastomas by the presence of both cystic and solid components on imaging.

References

- Pilocytic astrocytomas.
- Pediatric cerebellar astrocytoma: a review.
- Heterogeneity of histopathological presentation of pilocytic astrocytoma - diagnostic pitfalls. A review.

Settings

Item 36 of 40
Question Id: 615

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

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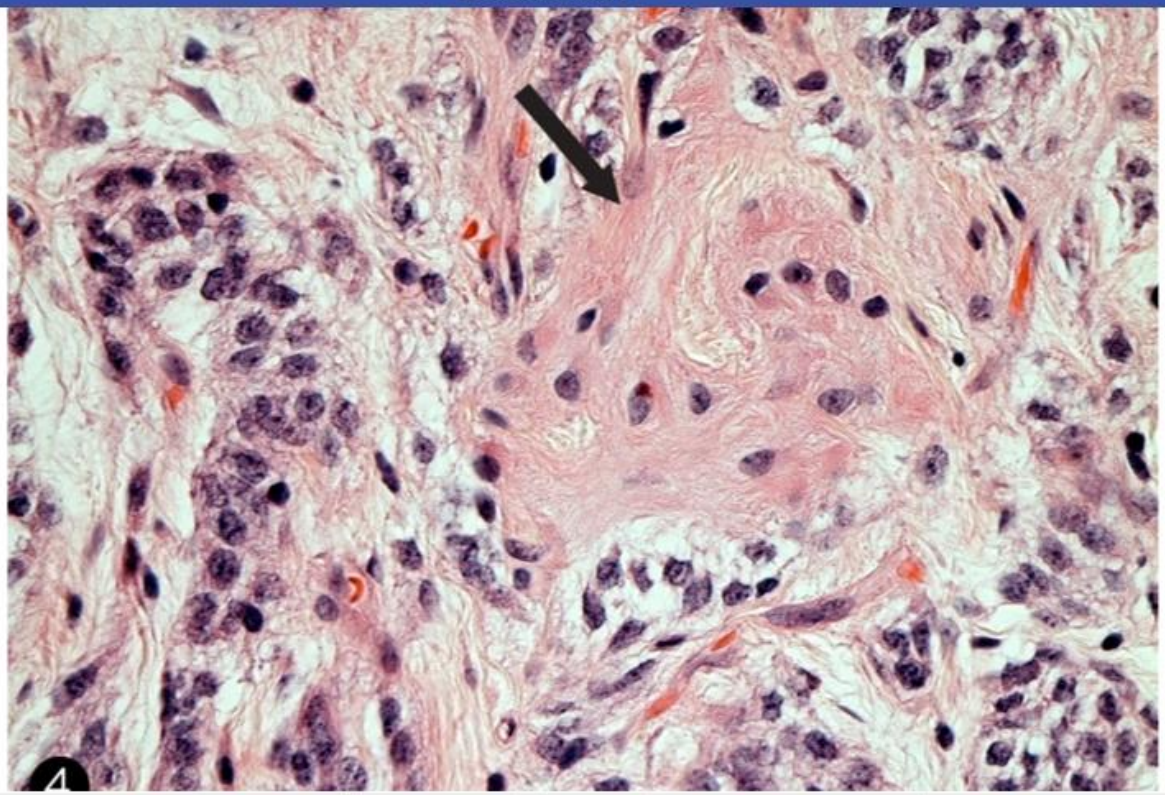

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(Choice D) Oligodendrogliomas, rare in children, are frequently calcified, well-circumscribed masses located in the frontal lobe. Microscopy

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2/10/2019

Settings

Item 37 of 40
Question Id: 1792

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

A 53-year-old female treated with high-dose folic acid for anemia experiences a moderate increase in her hemoglobin level. She returns to clinic complaining of bilateral foot numbness and difficulty in walking. The latter symptoms are most likely related to which of the following?

- A. Folate overdose
- B. Iron deficiency
- C. Cobalamin deficiency
- D. Hemolysis
- E. Aplastic anemia

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4:21 PM
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A 53-year-old female treated with high-dose folic acid for anemia experiences a moderate increase in her hemoglobin level. She returns to clinic complaining of bilateral foot numbness and difficulty in walking. The latter symptoms are most likely related to which of the following?

- A. Folate overdose [4%]
- B. Iron deficiency [1%]
- ✔ C. Cobalamin deficiency [90%]
- D. Hemolysis [1%]
- E. Aplastic anemia [1%]

Omitted
Correct answer
C

90%
Answered correctly

3 Seconds
Time Spent

08/27/2018
Last Updated

Explanation

The clinical decision to treat this patient with folic acid suggests that her anemia was megaloblastic and therefore likely secondary to a deficiency in folate and/or vitamin B_{12} (cobalamin). Her subsequent development of neurological symptoms (a finding not associated with folate deficiency alone) indicates that she is deficient in vitamin B_{12}.

A moderate improvement in the hemoglobin level often occurs when a deficiency in vitamin B_{12} is treated with folate, or vice versa. However, the

Explanation

The clinical decision to treat this patient with folic acid suggests that her anemia was megaloblastic and therefore likely secondary to a deficiency in folate and/or vitamin B_{12} (cobalamin). Her subsequent development of neurological symptoms (a finding not associated with folate deficiency alone) indicates that she is deficient in vitamin B_{12}.

A moderate improvement in the hemoglobin level often occurs when a deficiency in vitamin B_{12} is treated with folate, or vice versa. However, the treatment of vitamin B_{12} deficiency with folate will not reverse any neurologic dysfunction caused by the vitamin B_{12} deficiency. In fact, the usage of folate alone can worsen demyelination and cause abnormal myelin synthesis by depleting the concentration of unmethylated cobalamin available for methylmalonyl-CoA processing. The walking difficulties and paresthesias seen in this patient were therefore likely precipitated by the administration of folate alone.

(Choice A) High doses of folate may antagonize phenytoin, thereby precipitating seizures in a select group of patients. Walking difficulties and paresthesias are not typically associated with folate overdose, however.

(Choice B) Iron deficiency is characterized by a hypochromic, microcytic anemia that is best treated with iron supplementation. Walking difficulties and paresthesias are not typically associated with iron deficiency anemia.

(Choices D and E) Anemia of any cause can provoke nonspecific neurologic symptoms (eg, tinnitus, irritability, generalized weakness). Walking difficulties and paresthesias are not commonly associated with hemolysis or aplastic anemia, however.

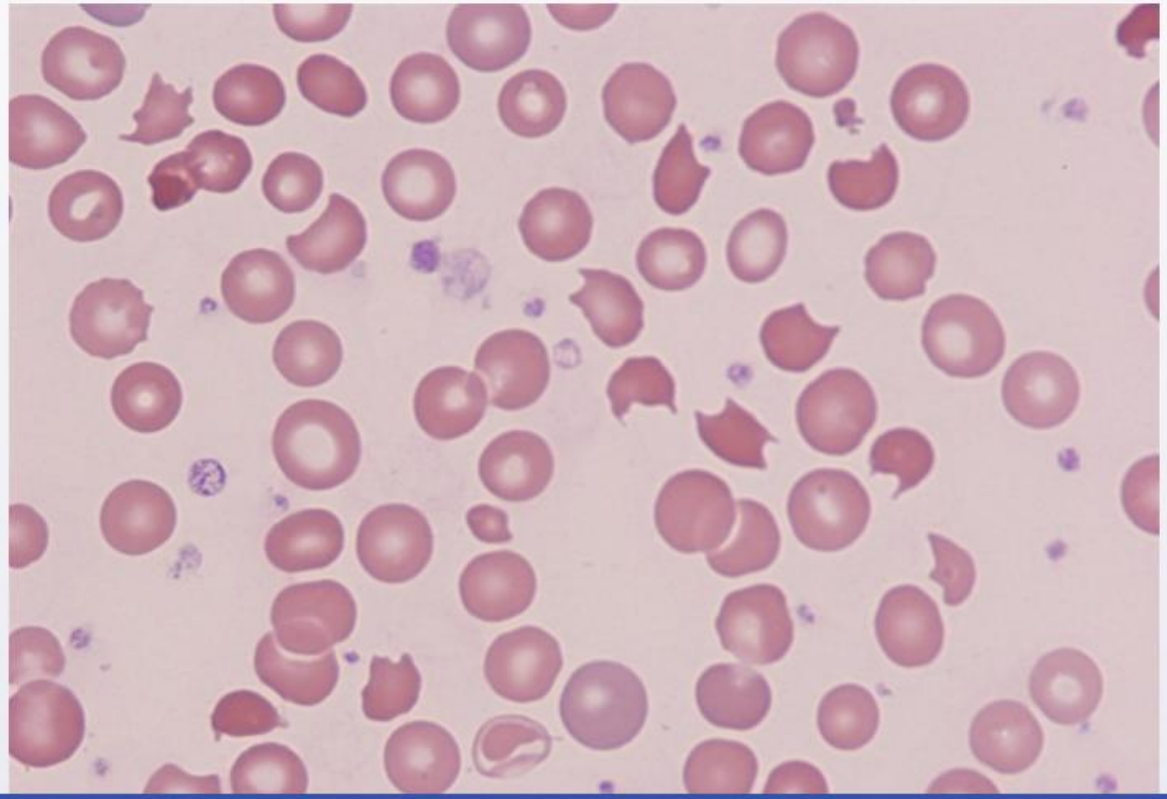
Educational Objective:
Deficiency of vitamin B_{12} is associated with both megaloblastic anemia and neurologic dysfunction, while folate deficiency is associated with megaloblastic anemia alone. Moderate improvement in the hemoglobin level often occurs when a deficiency in vitamin B_{12} is treated with folate, or vice versa. Treatment of vitamin B_{12} deficiency with folate alone can actually worsen neurologic dysfunction.

Settings

Item 38 of 40
Question Id: 1294

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

A 7-year-old boy comes to the office for follow-up. A week ago, the patient began having episodes of bloody diarrhea, and these have since resolved. Currently, laboratory studies show acute renal failure. A complete blood count shows anemia and thrombocytopenia. Coagulation studies are within normal limits. His peripheral blood smear is shown in the image below.



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2/10/2019

Settings

Item 38 of 40
Question Id: 1294

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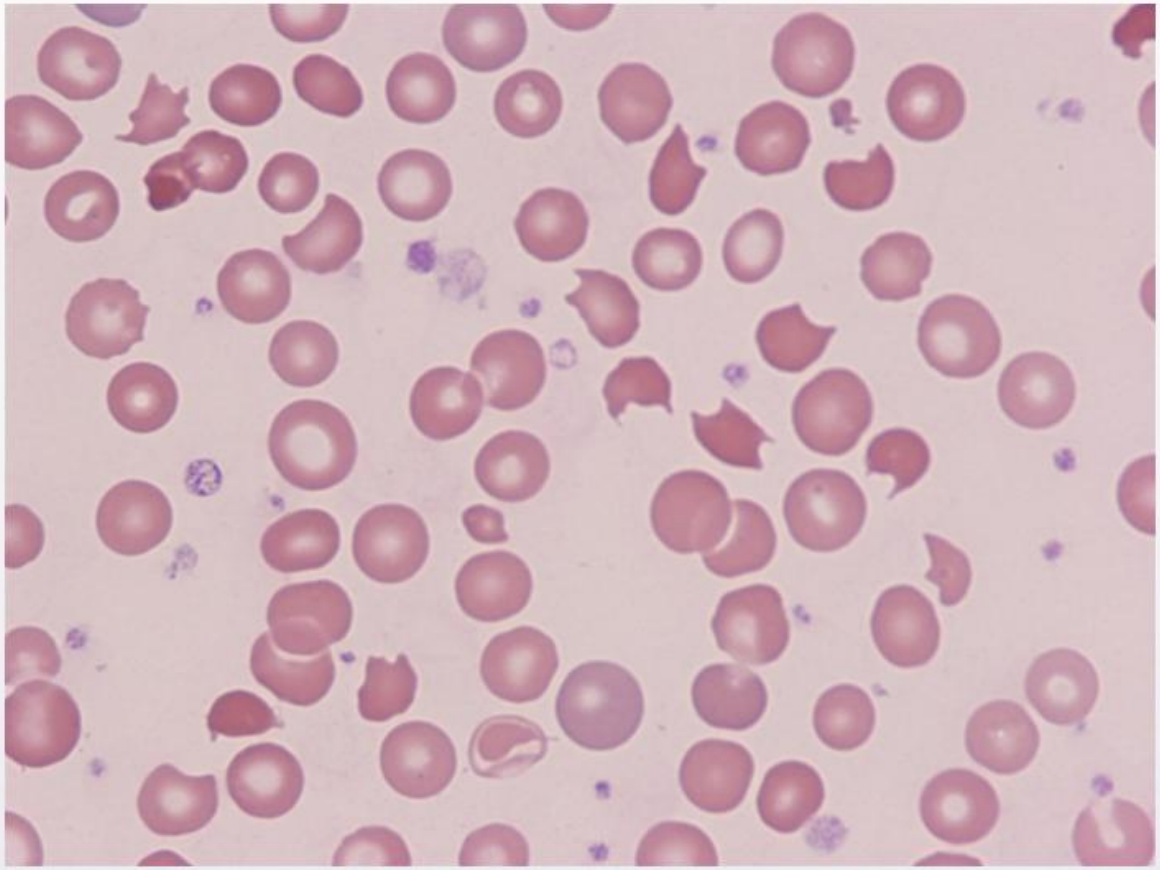

Which of the following is the most likely cause of this patient's anemia?

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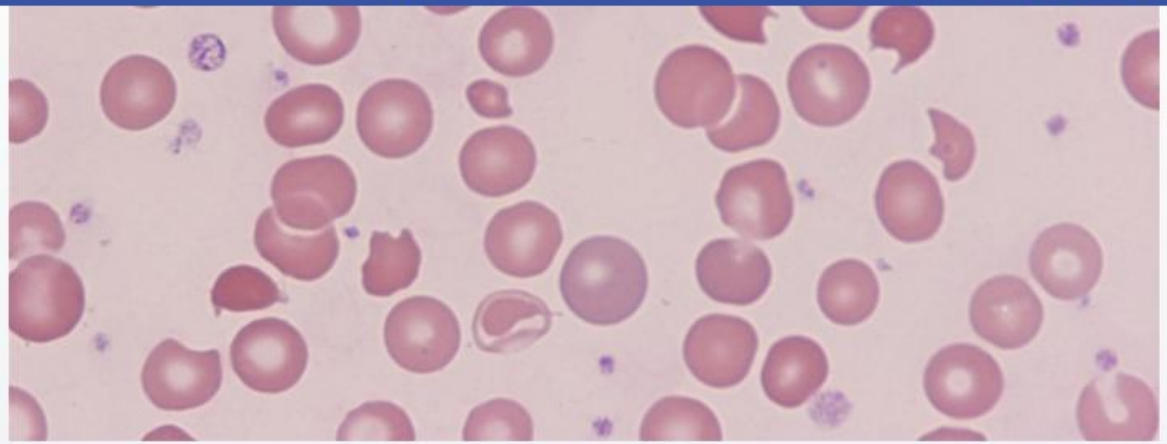
Settings

Item 38 of 40
Question Id: 1294

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



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

A. Autoimmune hemolytic anemia from a diarrheal organism
B. Erythropoietin deficiency from renal failure
C. Hemolytic anemia due to oxidative stress
D. Leukoerythroblastosis due to marrow fibrosis
E. Microangiopathic hemolytic anemia

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Item 38 of 40
Question Id: 1294

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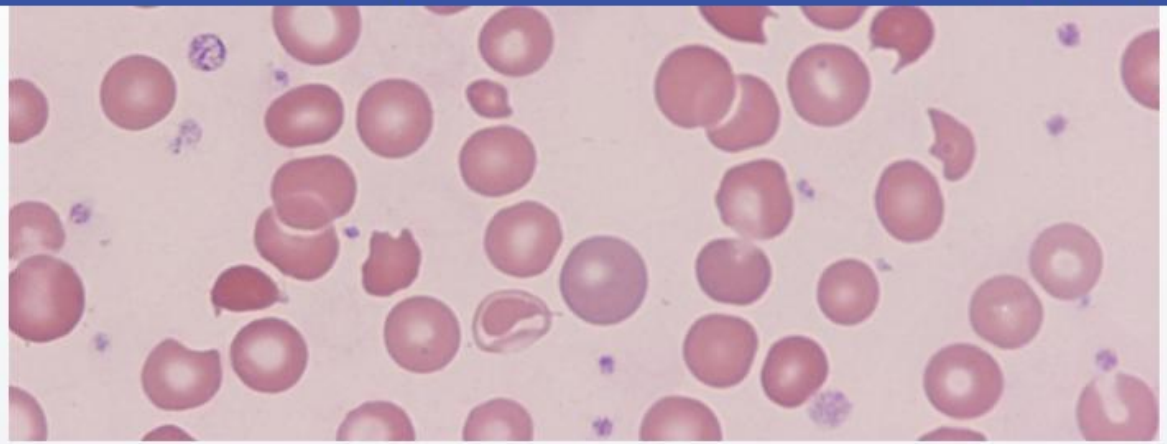

Which of the following is the most likely cause of this patient's anemia?

- A. Autoimmune hemolytic anemia from a diarrheal organism [23%]
- B. Erythropoietin deficiency from renal failure [1%]
- C. Hemolytic anemia due to oxidative stress [12%]
- D. Leukoerythroblastosis due to marrow fibrosis [0%]
- ✔ E. Microangiopathic hemolytic anemia [61%]

Omitted
Correct answer

61%
Answered correctly

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Item 38 of 40
Question Id: 1294

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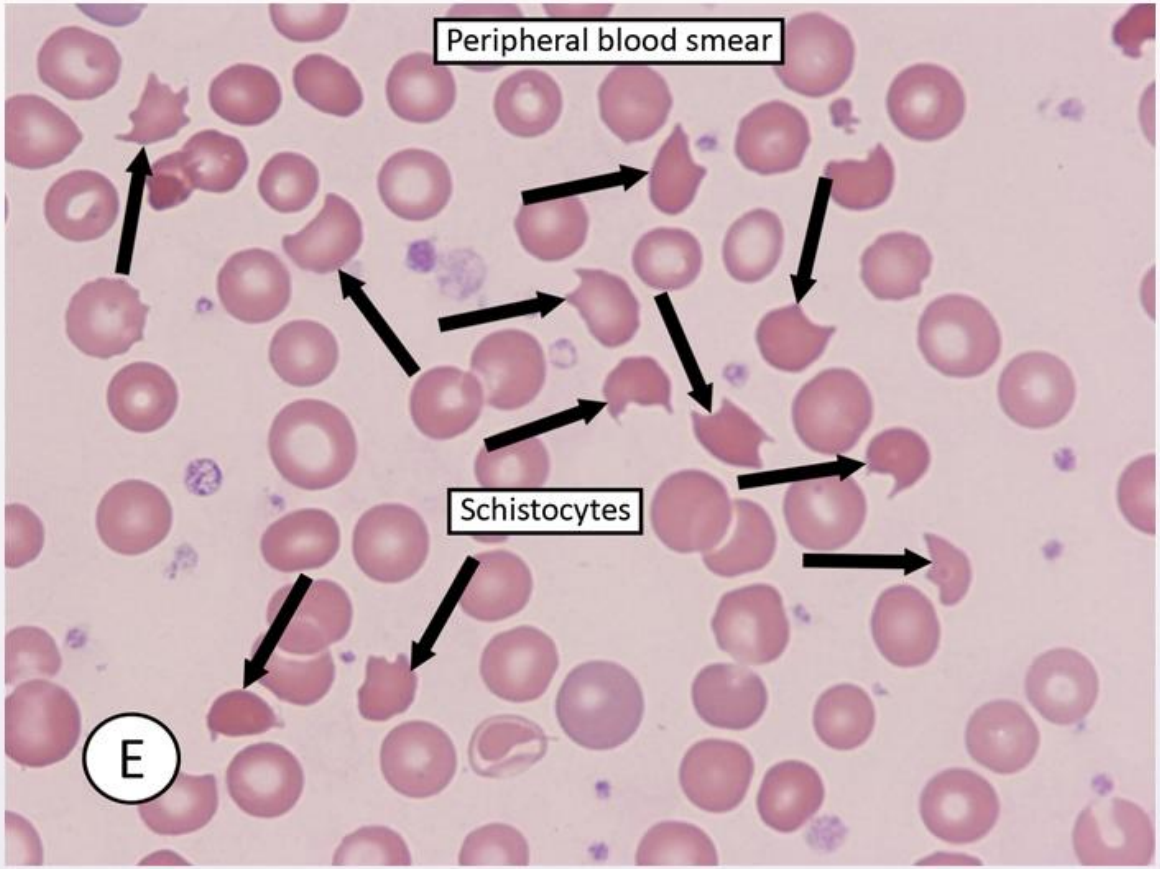

The clinical presentation and the peripheral blood smear shown are typical of **hemolytic uremic syndrome** (HUS). Most cases of childhood HUS

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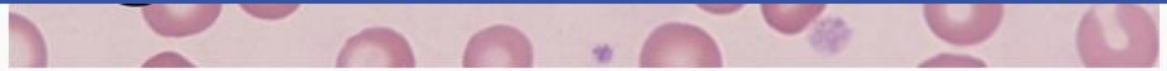

The clinical presentation and the peripheral blood smear shown are typical of **hemolytic uremic syndrome** (HUS). Most cases of childhood HUS are preceded by bloody diarrhea, often caused by Shiga-like toxin released from enterohemorrhagic *Escherichia coli* (particularly strain O157:H7). Undercooked ground beef is a common cause of HUS.

The smear contains classic **schistocytes** (fragmented red cells) and few platelets. Schistocytes are diagnostic of a traumatic mechanism and indicate either **microangiopathic hemolytic anemia** (eg, HUS, thrombotic thrombocytopenic purpura [TTP], disseminated intravascular coagulation [DIC], malignant hypertension, metastatic carcinoma) or mechanical damage (eg, prosthetic valve, severely calcified valves). HUS and TTP lie on a spectrum. Unlike in DIC, the coagulation system is not activated in HUS-TTP; therefore, coagulation studies (prothrombin time and partial thromboplastin time) are normal, as seen with this patient.

(Choice A) Autoimmune hemolytic anemia (AIHA) is due to an altered immune response and the production of antibodies against erythrocytes. AIHA can occur following infections with *Mycoplasma pneumoniae* and Epstein-Barr virus but not usually following a diarrheal illness. In addition, thrombocytopenia and renal failure are not associated with AIHA.

(Choice B) Erythropoietin deficiency from renal failure results in normocytic, normochromic anemia; neither schistocytes nor decreased platelets are present. Erythropoietin deficiency is usually seen in chronic renal failure; this patient has acute renal failure.

(Choice C) Glucose-6-phosphate dehydrogenase (G6PD) deficiency anemia causes hemolytic anemia due to oxidative stress. It is not associated with thrombocytopenia or renal failure. The peripheral smear usually shows "bite cells."

(Choice D) Leukoerythroblastic peripheral smears demonstrate nucleated red cells and immature white cells. This is usually seen when the marrow is replaced with fibrosis (or metastatic cancer). The red cells can be squeezed while passing through these fibrous strands and appear on the peripheral smear as characteristic **teardrop cells**.

Educational objective:
Schistocytes suggest microangiopathic hemolytic anemia (eg, hemolytic-uremic syndrome [HUS], thrombotic thrombocytopenic purpura [TTP], disseminated intravascular coagulation [DIC]) or mechanical damage (eg, prosthetic valve]). In childhood, HUS is often preceded by bloody

coagulation [DIC], malignant hypertension, metastatic carcinoma) or mechanical damage (eg, prosthetic valve, severely calcified valves). HUS and TTP lie on a spectrum. Unlike in DIC, the coagulation system is not activated in HUS-TTP; therefore, coagulation studies (prothrombin time and partial thromboplastin time) are normal, as seen with this patient.

(Choice A) Autoimmune hemolytic anemia (AIHA) is due to an altered immune response and the production of antibodies against erythrocytes. AIHA can occur following infections with *Mycoplasma pneumoniae* and Epstein-Barr virus but not usually following a diarrheal illness. In addition, thrombocytopenia and renal failure are not associated with AIHA.

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(Choice C) Glucose-6-phosphate dehydrogenase (G6PD) deficiency anemia causes hemolytic anemia due to oxidative stress. It is not associated with thrombocytopenia or renal failure. The peripheral smear usually shows "bite cells."

(Choice D) Leukoerythroblastic peripheral smears demonstrate nucleated red cells and immature white cells. This is usually seen when the marrow is replaced with fibrosis (or metastatic cancer). The red cells can be squeezed while passing through these fibrous strands and appear on the peripheral smear as characteristic **teardrop cells**.

Educational objective:
Schistocytes suggest microangiopathic hemolytic anemia (eg, hemolytic-uremic syndrome [HUS], thrombotic thrombocytopenic purpura [TTP], disseminated intravascular coagulation [DIC]) or mechanical damage [eg, prosthetic valve]). In childhood, HUS is often preceded by bloody diarrhea. Coagulation studies (prothrombin time and partial thromboplastin time) are normal in HUS-TTP but abnormal in DIC.

References

- Thrombotic microangiopathies: thrombotic thrombocytopenic purpura/hemolytic uremic syndrome.

Settings

Item 38 of 40
Question Id: 1294

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

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Hemolytic uremic syndrome	
Etiology	Shiga toxin-producing bacteria • *Escherichia coli* O157:H7 • *Shigella*
Clinical features	• Antecedent diarrheal illness (often bloody) • Hemolytic anemia with schistocytes • Thrombocytopenia • Acute kidney injury

Zoom In | Zoom Out | Reset | Add To Flash Card

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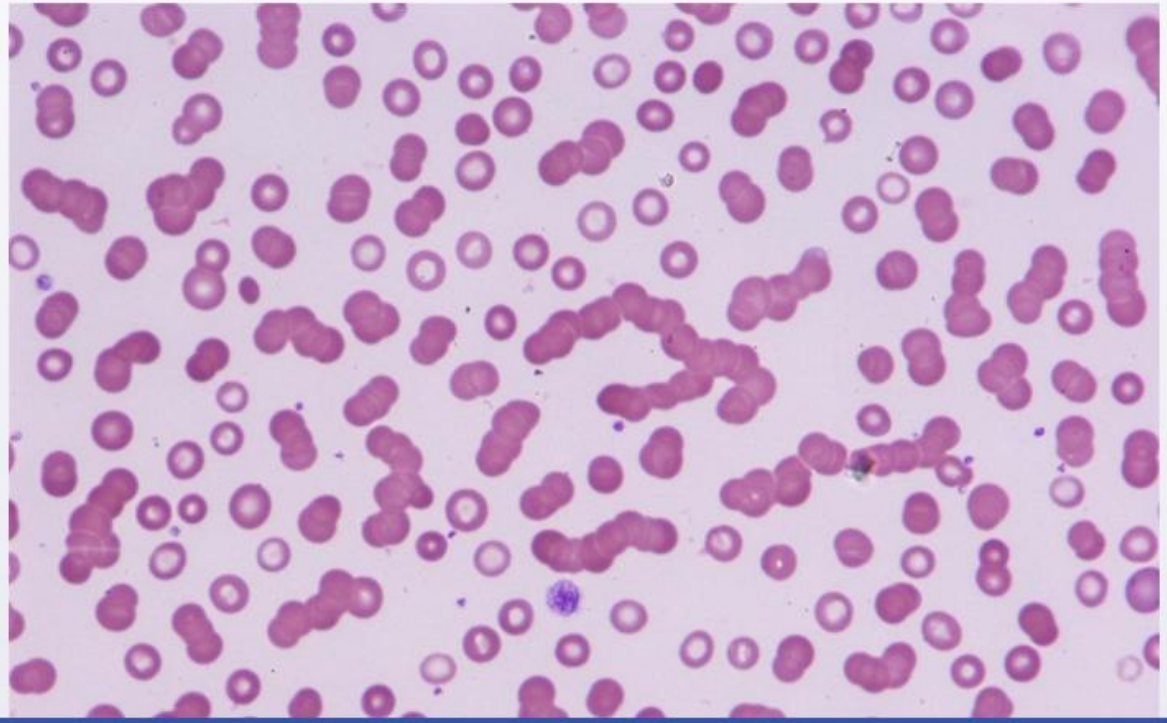
Settings

Item 39 of 40
Question Id: 6530

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

A 65-year-old man comes to the office due to 4 months of worsening fatigue. The patient feels tired with simple household chores. He has a 15-pack-year smoking history and drinks 2 or 3 beers daily. Temperature is 37 C (98.6 F), blood pressure is 134/86 mm Hg, and pulse is 76/min. Physical examination reveals a late systolic ejection murmur with a soft S2. The lungs are clear to auscultation. The abdomen is soft and nontender with no hepatosplenomegaly. There are no focal neurological deficits. Laboratory testing reveals hemoglobin is 9 g/dL and mean corpuscular volume is 93 μm^3. Peripheral blood smear is shown below:



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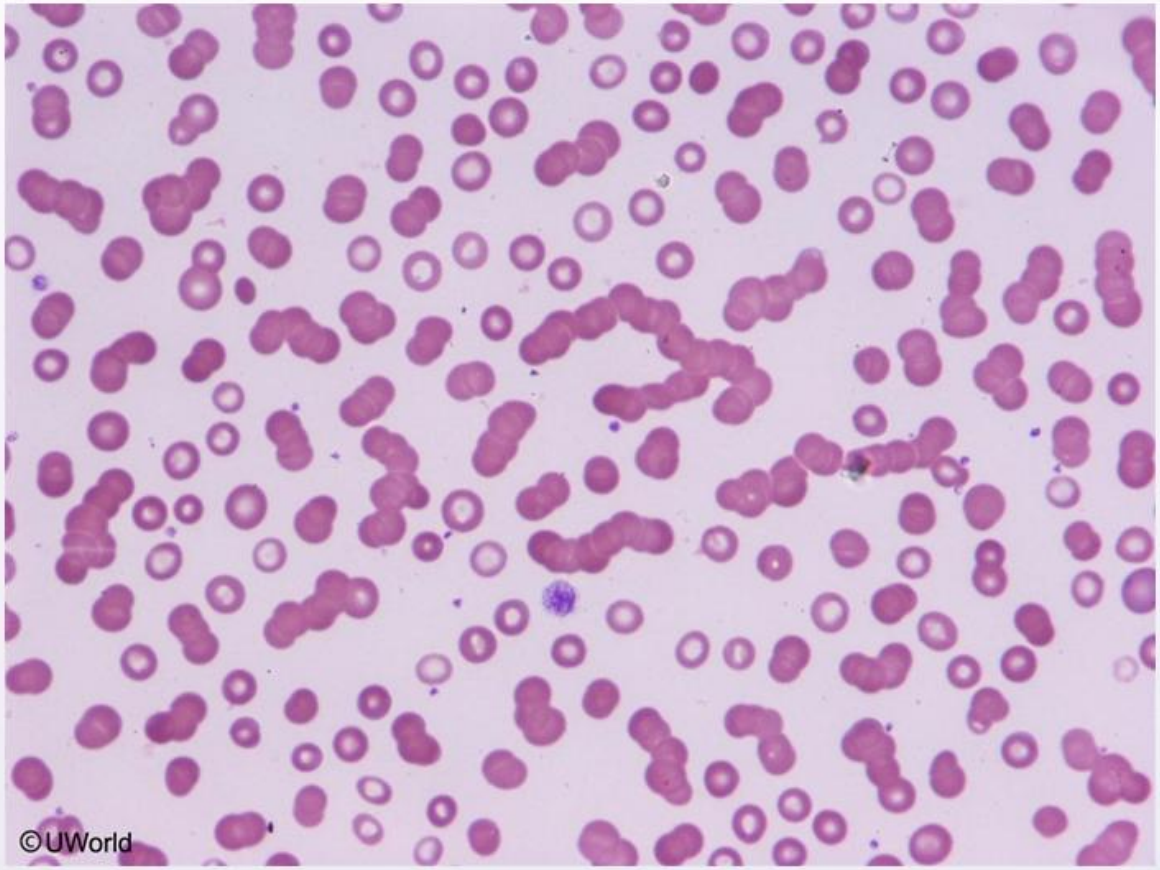
Settings

Item 39 of 40
Question Id: 6530

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



Which of the following best explains the observed erythrocyte findings in this patient?

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Block Time Remaining: 00:04:14
TUTOR

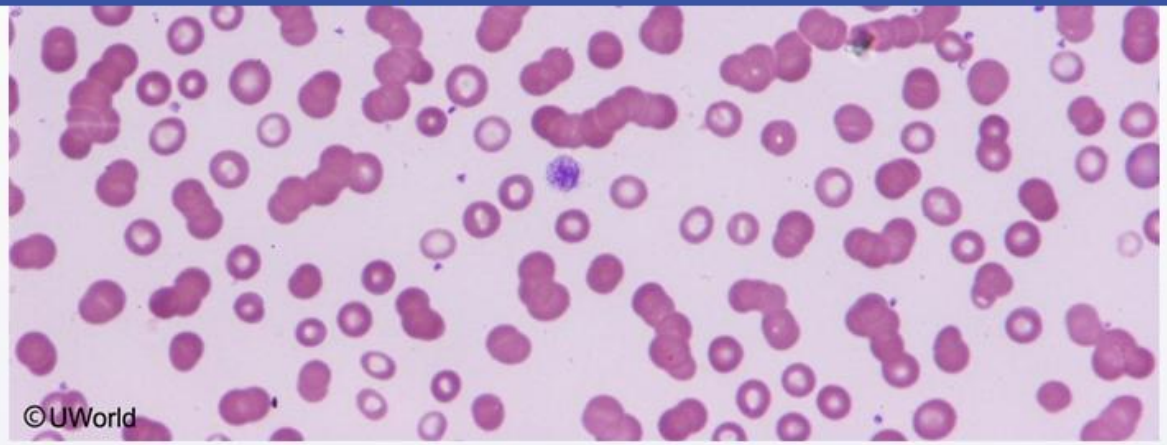
10 | Feedback | Suspend | End Block

4:21 PM
2/10/2019

Settings

Item 39 of 40
Question Id: 6530

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



Which of the following best explains the observed erythrocyte findings in this patient?

- A. Chronic gastrointestinal blood loss
- B. Excessive cold agglutinin production
- C. Increased serum paraproteins
- D. Mechanical erythrocyte injury
- E. Nutritional vitamin B_{12} deficiency

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Block Time Remaining: 00:04:16
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13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40

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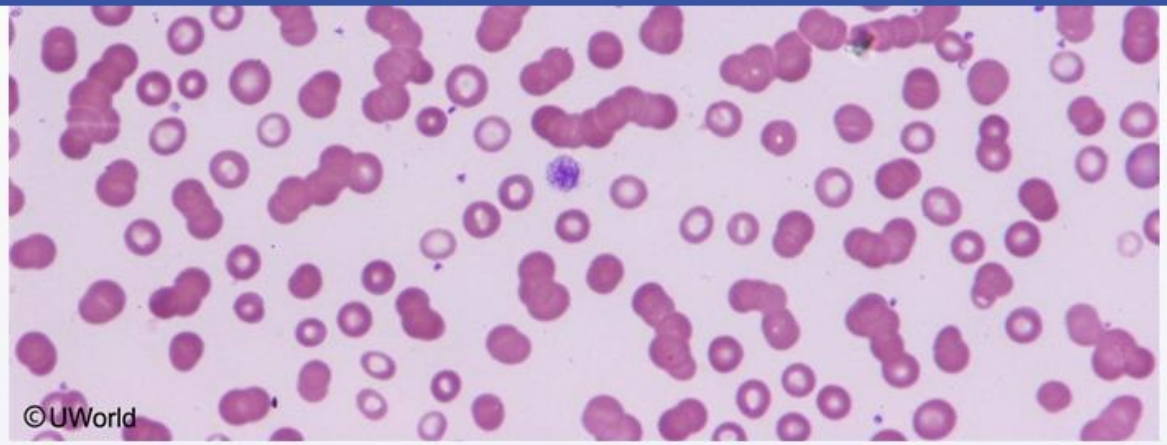
2/10/2019

Settings

Item 39 of 40
Question Id: 6530

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



Which of the following best explains the observed erythrocyte findings in this patient?

- A. Chronic gastrointestinal blood loss [9%]
- B. Excessive cold agglutinin production [25%]
- ✔ C. Increased serum paraproteins [56%]
- D. Mechanical erythrocyte injury [5%]
- E. Nutritional vitamin B_{12} deficiency [2%]

Omitted
Correct answer

56%
Answered correctly

9 Seconds
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12/08/2018
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Block Time Remaining: 00:04:18
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13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40

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2/10/2019

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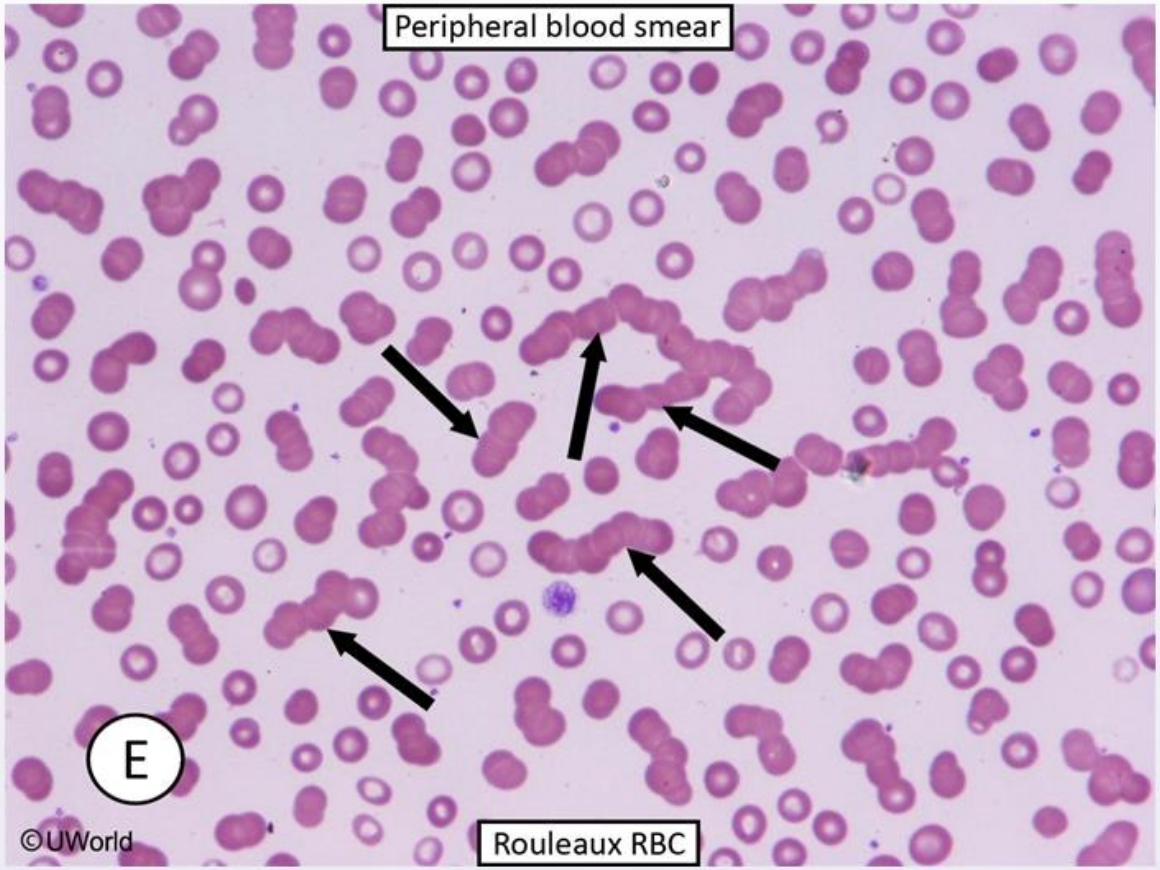
Item 39 of 40
Question Id: 6530

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



This patient's peripheral blood smear shows rows of erythrocytes stacked on one another like coins (**rouleaux formation**). This occurs due to elevated levels of **circulating proteins**, which disrupts the repulsive electrostatic charge on the erythrocyte surface and causes stacked

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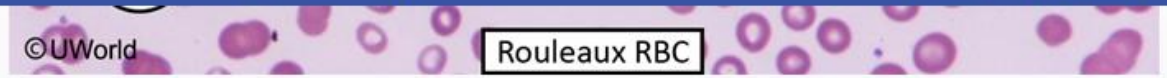
2/10/2019



This patient's peripheral blood smear shows rows of erythrocytes stacked on one another like coins (**rouleaux formation**). This occurs due to elevated levels of **circulating proteins**, which disrupts the repulsive electrostatic charge on the erythrocyte surface and causes stacked aggregation. Although rouleaux formation can be seen with inflammatory conditions (eg, infection, rheumatic disease) that increase acute-phase reactants (eg, fibrinogen), it is classically linked to lymphoproliferative/plasma cell disorders such as **multiple myeloma** and Waldenstrom macroglobulinemia, which generate high levels of **monoclonal paraprotein** (immunoglobulins).

Multiple myeloma is a plasma cell malignancy often associated with **normocytic anemia**, osteolytic bone lesions, and hypercalcemia due to proliferation of neoplastic cells in the bone marrow. Patients also frequently have renal insufficiency (due to immunoglobulin light-chain cast nephropathy) and nonspecific symptoms (eg, fatigue). Elevated circulating levels of monoclonal immunoglobulin cause rouleaux formation in >50% of cases. Diagnosis is generally made using serum/urine protein electrophoresis (monoclonal M-spike) and bone marrow biopsy.

(Choice A) Chronic gastrointestinal blood loss is a leading cause of iron-deficiency anemia, which usually results in microcytosis and **hypochromia** on peripheral smear (sometimes with target cells). Rouleaux formation is not a typical feature, and normocytic anemia is uncommon.

(Choice B) Cold agglutinins are cross-reactive IgM antibodies that form with some infections (particularly *Mycoplasma pneumoniae*) and hematologic malignancies. Cold agglutinins typically cause **clumping agglutination** (not stacked-coin agglutination) and intravascular hemolysis.

(Choice D) Mechanical erythrocyte injury is common in patients with damaged or artificial heart valves. Although this patient has a cardiac murmur that indicates possible aortic stenosis, mechanical erythrocyte injury is usually associated with **schistocytes** on peripheral blood smear, not rouleaux formation.

(Choice E) Vitamin B_{12} deficiency causes abnormal hematologic cell nuclear maturation, which leads to macrocytic anemia and **hypersegmented neutrophils** on peripheral blood smear.

Educational objective:

aggregation. Although rouleaux formation can be seen with inflammatory conditions (eg, infection, rheumatic disease) that increase acute-phase reactants (eg, fibrinogen), it is classically linked to lymphoproliferative/plasma cell disorders such as **multiple myeloma** and Waldenstrom macroglobulinemia, which generate high levels of **monoclonal paraprotein** (immunoglobulins).

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(Choice E) Vitamin B_{12} deficiency causes abnormal hematologic cell nuclear maturation, which leads to macrocytic anemia and **hypersegmented neutrophils** on peripheral blood smear.

Educational objective:
Multiple myeloma is associated with elevated circulating paraproteins (monoclonal immunoglobulins), which causes erythrocytes to stack like coins (rouleaux formation). Patients classically have normocytic anemia, hypercalcemia, bone pain, and renal insufficiency.

Settings

Item 40 of 40
Question Id: 1572

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

A 56-year-old man comes to the office due to several months of progressive neck swelling. He has also had intermittent epistaxis and headaches. The patient has no chronic medical conditions and takes no medications. He does not use tobacco, alcohol, or illicit drugs, and he emigrated to the United States from rural China 12 years ago. Physical examination shows several enlarged, firm, and nontender cervical lymph nodes. Nasopharyngeal evaluation reveals a mass arising from the pharyngeal recess. Histopathological examination of the mass shows undifferentiated malignant cells of epithelial origin. Further analysis of these cells is most likely to reveal the presence of nucleic acid sequences from which of the following viruses?

- A. Adenovirus
- B. Coronavirus
- C. Cytomegalovirus
- D. Epstein-Barr virus
- E. Human herpes virus 8
- F. Polyomavirus

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13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40

4:22 PM
2/10/2019

Settings

Item 40 of 40
Question Id: 1572

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

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- A. Adenovirus [1%]
- B. Coronavirus [0%]
- C. Cytomegalovirus [2%]
- ✔ D. Epstein-Barr virus [90%]
- E. Human herpes virus 8 [3%]
- F. Polyomavirus [1%]

Omitted
Correct answer
D

90%
Answered correctly

3 Seconds
Time Spent

12/06/2018
Last Updated

Explanation

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Block Time Remaining: 00:04:21
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Explanation

Nasopharyngeal carcinoma is an epithelial tumor that usually originates in the pharyngeal recess. Local tumor growth often leads to epistaxis and headaches, and metastatic spread to cervical lymph nodes frequently causes firm, fixed neck swelling. NPC is relatively uncommon in the United States but is endemic to **southern China**, where genetic and dietary factors (eg, consumption of salted fish) predispose to premalignant nasopharyngeal epithelial lesions. Subsequent **malignant transformation** is then induced by **Epstein-Barr virus** (EBV).

EBV is a ubiquitous human herpes virus that causes infectious mononucleosis in a minority of patients (primary infection is usually asymptomatic). Initial infection is followed by life-long **latent infection** in memory B cells. While latent, the EBV genome exists as an episome in the nucleus of infected cells and expresses a restricted subset of EBV genes (**latency genes**) which do the following:

- Promote periodic viral reactivation from memory B-cells, leading to recurrent (asymptomatic) mucosal infections.
- Promote survival of infected memory B cells by encoding for proteins (eg, EBNA-1, LMP1) that prevent apoptosis. In a minority of patients, these proteins are oncogenic and lead to **malignant transformation** of infected B cells (eg, Burkitt lymphoma, Hodgkin lymphoma) or premalignant epithelial cells (eg, nasopharyngeal carcinoma, salivary cancer).

Individuals who do not have premalignant epithelial lesions are at very low risk of EBV-associated epithelial cancers like NPC.

(Choice A) Adenovirus causes acute upper respiratory infection with pharyngitis, coryza, otitis media, bronchitis, and/or pneumonia. It is not associated with nasopharyngeal carcinoma.

(Choice B) Coronavirus is one of the most common causes of upper respiratory tract infection (eg, common cold) but has no association with nasopharyngeal or other cancers.

(Choices C and E) Cytomegalovirus (CMV) and human herpes virus 8 (HHV-8) are also herpes viruses; as such, they cause acute infection followed by latent disease. Although CMV can reactivate in immunocompromised individuals (eg, HIV, post-transplantation) and cause severe

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(Choices C and E) Cytomegalovirus (CMV) and human herpes virus 8 (HHV-8) are also herpes viruses; as such, they cause acute infection followed by latent disease. Although CMV can reactivate in immunocompromised individuals (eg, HIV, post-transplantation) and cause severe end-organ disease (eg, retinitis, gastroenteritis), it is not an oncogenic virus. HHV-8 reactivation also primarily occurs in immunocompromised individuals and is associated with Kaposi sarcoma.

(Choice F) The BK and JC viruses are members of Polyomaviridae and cause life-long latent infections in the kidney. BK reactivation can cause nephropathy in renal transplant recipients, and JC virus causes progressive multifocal leukoencephalopathy (primarily in patients with advanced HIV).

Educational objective:
Nasopharyngeal cancer is endemic in southern China due to genetic and dietary factors that promote nasopharyngeal epithelial pre-malignant lesions. In almost all cases, malignant transformation occurs due to infection of premalignant cells with Epstein-Barr virus and the subsequent expression of oncogenic viral proteins.