46-Year-Old Man With Fevers, Chills, and Pancytopenia

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A 46-year-old man from Minnesota presented to his primary care physician with a 2-week history of furuncle on his abdomen that was gradually increasing in size and had started to produce purulent drainage. Physical examination revealed a firm 4-cm lesion with a small amount of surrounding erythema and induration in the left lower abdominal quadrant. He did not report any recent travel, animal exposures, tick bites, or sick contacts. His medical history was significant for hypothyroidism and dyslipidemia, and he had no known drug allergies.

1. **According to the Infectious Diseases Society of America (IDSA) guidelines, which would be the *best* antibiotic for this patient?**
   a. Trimethoprim-sulfamethoxazole
   b. Cephalexin
   c. Amoxicillin-clavulanate
   d. Metronidazole
   e. Ciprofloxacin

Consensus guidelines from the IDSA recommend routine treatment for community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) in patients presenting with purulent cellulitis.[1] Our patient has purulent cellulitis and therefore should be treated for community-acquired MRSA. Trimethoprim-sulfamethoxazole (Bactrim) has good coverage for community-acquired MRSA and would be recommended in this scenario. Cephalexin (Keflex), amoxicillin-clavulanate (Augmentin), metronidazole (Flagyl), and ciprofloxacin (Cipro) are not active against MRSA and thus would not be appropriate treatments for this patient.

The patient was given 2 tablets of double-strength trimethoprim-sulfamethoxazole twice daily. Wound cultures were obtained and yielded MRSA, which was susceptible to trimethoprim-sulfamethoxazole. The abscess spontaneously drained and decreased in size during the next few days. However, the patient developed fevers and a new rash while receiving antibiotic therapy and contacted his physician for follow-up. At this point, he had received trimethoprim-sulfamethoxazole for 6 days. Because of concern that infection was not responding to oral antibiotic, he was admitted to the hospital for intravenous antibiotic therapy.

On examination, his vital signs were within the reference range, with the exception of a temperature of 39.2°C. Heart and lung examination findings were normal. The patient was noted to have a 3-cm area of induration with a central opening in the left lower abdominal wall. There was no appreciable lymphadenopathy or splenomegaly. His skin examination was significant for diffuse petechiae.

Admission work-up yielded the following results (reference ranges provided parenthetically): hemoglobin, 13 g/dL (13.5-17.5 g/dL; to convert to g/L, multiply by 10); white blood cell count, 2×10^9/L ($3.5\text{-}10.5 \times 10^9$/L); platelet count, 2×10^9/L ($1.5\text{-}4.5 \times 10^9$/L); absolute neutrophil count, 1.2×10^9/L ($>1.5 \times 10^9$/L); creatinine, 1.2 mg/dL (0.8-1.3 mg/dL; to convert to μmol/L, multiply by 88.4); sodium, 134 mmol/L (135-145 mmol/L); aspartate aminotransferase, 226 U/L (8-48 U/L); alanine aminotransferase, 149 U/L (7-55 U/L); erythrocyte sedimentation rate, 33 mm/h (0-22 mm/h); and C-reactive protein, 20.9 mg/L (≤8 mg/L; to convert to nmol/L, multiply by 9.524). Computed tomography of the abdomen and pelvis revealed mild splenomegaly and inflammatory stranding in the subcutaneous tissue of the left lower abdominal wall, with no drainable fluid collection or evidence of intra-abdominal extension.

2. **Besides a peripheral smear, what would be the *next best* diagnostic study?**
   a. Ferritin and triglyceride levels
   b. Cytomegalovirus (CMV) IgM and IgG
   c. Bone marrow biopsy
   d. Parvovirus B19 IgM
   e. Lyme enzyme-linked immunosorbent assay (ELISA)

Ferritin and triglyceride levels are often elevated in hemophagocytic syndrome (hemophagocytic lymphohistiocytosis). This is a hyperinflammatory condition with prolonged fever, splenomegaly, cytopenias (involving ≥2 cell lines), and hemophagocytosis by activated benign macrophages.[2] However, this is a rare cause of pancytopenia and could be considered if more common causes are ruled out. Cytomegalovirus infection usually causes a mononucleosislike illness in immunocompetent hosts, like our patient. Thus, acute CMV infection is quite unlikely in this case. Bone marrow biopsy is often indicated in patients with pancytopenia to differentiate between intrinsic and extrinsic causes, such as hematologic malignancies. Common hematologic neoplasms causing pancytopenia include plasma cell myeloma, myelodysplastic syndrome (MDS),

See end of article for correct answers to questions.

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and non-Hodgkin lymphoma.[3] Parvovirus-associated arthropathy usually presents with acute-onset symmetric polyarticular arthritis, with the proximal interphalangeal and metacarpophalangeal joints most commonly affected.[4] However, the most common hematologic complication associated with parvovirus is pure red blood cell aplasia. Our patient does not have arthritis and has slight anemia, making parvovirus unlikely. ELISA tests for Lyme disease. Our patient has no known tick exposure, and his clinical presentation is not consistent with Lyme disease.

A peripheral blood smear was obtained and the result was negative for any evidence of acute leukemia, schistocytes, or platelet clumping. Further testing for disseminated intravascular coagulation (DIC) was performed, and the results were as follows: D-dimer, 565 ng/mL (≤250 ng/mL); fibrinogen, 428 mg/dL (200-375 mg/dL; to convert to μmol/L, multiply by 0.0294); fibrinogen equivalent units, 1.13 μg/mL (≤0.5 μg/mL); prothrombin time, 14.2 seconds (9.5-13.8 seconds); international normalized ratio (INR), 1.2 (0.8-1.2); and partial thromboplastin time, 48 seconds (28-38 seconds).

3. **Considering our patient's clinical presentation and laboratory findings, which *one* of the following statements is *false*?**
   a. Infection can trigger the development of DIC
   b. INR is usually elevated in DIC
   c. Fibrinogen level can be elevated as an acute-phase reactant
   d. D-dimer level is usually low in DIC
   e. DIC can be associated with a high mortality

There are many triggers for DIC, with sepsis being the most common. Besides infection, other triggers for DIC include malignancy, pregnancy, liver disease, and hemophagocytosis syndrome. A clinical diagnosis of DIC is based on consistent clinical presentation coupled with laboratory results, specifically low platelet count, elevated fibrin-related marker (soluble fibrin monomers or fibrin degradation products), elevated prothrombin time, and low fibrinogen level. However, the fibrinogen level can also be elevated as an acute-phase reactant. D-dimer is usually high, not low, in DIC. The mortality for DIC ranges from 43% to 48% as compared with those without.[5] The International Society on Thrombosis and Haemostasis DIC score can be calculated based on platelet count (>100 = 0, <100 = 1, <50 = 2), fibrinogen level (>100 mg/dL = 0, <100 mg/dL = 1), prothrombin time (<15 seconds = 0, >15 seconds = 1, >18 seconds = 2), and D-dimer (<301 ng/mL = 0, >301 ng/mL = 1, >400 ng/mL = 2). A score of 5 or higher indicates overt DIC.[5]

Our patient's ferritin and triglyceride levels were within the reference range, and parvovirus IgG and IgM antibody test results were also negative. Blood cultures had no growth. Test results for other infectious agents were as follows: Epstein-Barr virus (EBV) IgG, positive; EBV IgM, negative; CMV polymerase chain reaction (PCR) in whole blood, undetectable; human immunodeficiency virus (HIV) serologic test and PCR, negative; and viral hepatitis panel, negative. Bone marrow biopsy was performed, and the specimen revealed slight hypocellularity with mild erythroid and granulocytic hypoplasia.

4. **On the basis of these test results, which *one* of the following is the *most likely* cause of this patient's pancytopenia?**
   a. Drug toxicity
   b. Hairy cell leukemia
   c. Reactivation of EBV infection
   d. Sepsis syndrome
   e. MDS

Drug-induced pancytopenia is a diagnosis of exclusion and should be considered once infection or malignant neoplasm has been excluded. There was no evidence of hairy cell leukemia on the peripheral blood smear or the bone marrow biopsy. The EBV serologic test findings were suggestive of a past infection, with a positive IgG and a negative IgM test result. Sepsis is classified as meeting criteria for systemic inflammatory response syndrome (SIRS) in the setting of suspected infection.[6] Our patient did not meet SIRS criteria. Moreover, his abscess was limited to the abdominal wall, without evidence of deeper extension on imaging, and blood cultures were negative. These findings make sepsis syndrome highly unlikely. Myelodysplastic syndrome encompasses a diverse group of malignant stem cell disorders that are characterized by dysplastic and ineffective blood cell production.[7] Myelodysplastic syndrome is diagnosed based on the peripheral blood smear and bone marrow biopsy findings. Because work-up results for both infectious and hematologic causes were negative, the patient's recent use of trimethoprim-sulfamethoxazole was considered the most likely cause of his pancytopenia.

Because of high suspicion of drug toxicity, trimethoprim-sulfamethoxazole was discontinued at admission. Because of severe thrombocytopenia and easy bruising, the patient was given platelet transfusions. Repeated testing 1 week after discharge revealed improvement in blood counts: hemoglobin, 11.5 g/dL (13.5-17.5 g/dL); white blood cell count, 5.4×10^9/L ($3.5\text{-}10.5 \times 10^9$/L); and platelet count, 143×10^9/L ($150\text{-}450 \times 10^9$/L).

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5. **Which *one* of the following is an adverse effect of trimethoprim-sulfamethoxazole therapy?**
   a. Flulike syndrome
   b. Hemorrhagic cystitis
   c. Nephrogenic diabetes insipidus
   d. Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
   e. Hyperkalemia

Flulike syndrome can occur with the use of interferon alfa 2b, which is used for treatment of hepatitis B or C. Hemorrhagic cystitis is most commonly associated with the use of cyclophosphamide. Nephrogenic diabetes insipidus can be seen with long-term lithium use. Drugs commonly associated with SIADH include selective serotonin reuptake inhibitors, chlorpropamide and carbamazepine. Patients receiving trimethoprim-sulfamethoxazole therapy can develop hyperkalemia due to blockade of the renal tubular sodium channels by the trimethoprim component, a mechanism similar to the action of potassium-sparing diuretics.[8] Trimethoprim also interferes with and reduces renal tubular secretion of creatinine, which can lead to an elevation in serum creatinine.[9] Hyperkalemia and elevation in serum creatinine levels resolve after trimethoprim-sulfamethoxazole therapy is discontinued and do not result in permanent renal dysfunction.

DISCUSSION

Pancytopenia is a term used to describe reduction in all blood cell lines. Optimal work-up of pancytopenia includes detailed history taking, meticulous physical examination, and judicious use of laboratory investigations in the clinical context. The differential diagnosis can be divided into 2 categories: intrinsic (decreased production) and extrinsic (peripheral destruction). To differentiate between the two, a reticulocyte count would be helpful. If the reticulocyte count is high, consider hemolysis or blood loss; if the reticulocyte count is low, consider deficiency in production. Peripheral blood smear provides a window into the functional status of the bone marrow and is crucial in the diagnosis of cytopenias. Worrisome findings include blast cells (Auer rods in acute myeloid leukemia [AML]), tumor cells (lymphoma), smudge cells (chronic lymphocytic leukemia), pigmented inclusions (malaria), and organisms (ehrlichiosis or anaplasmosis).

Intrinsic causes of pancytopenia include lack of nutrients (severe folate and cobalamin deficiency), medications (antibiotics and chemotherapy), and bone marrow disorders (acute leukemia, MDS, non-Hodgkin lymphoma [NHL], and pure red blood cell aplasia). Acute leukemia is the third most common cause of pancytopenia in general, and in adults AML is the most common type.[3] Clinical manifestations of AML are nonspecific and include generalized fatigue, pallor, weakness, and occasionally fever. Patients with MDS are typically asymptomatic. Clinical presentation in symptomatic patients varies, depending on which cell lineage is affected. Patients can present with fatigue, weakness, angina, and exercise intolerance (anemia) or a frequent or severe course of infections (leukopenia or neutropenia) or easy bruising and bleeding (thrombocytopenia). The clinical presentation of NHL is variable and, in large part, depends on the type of lymphoma. Indolent lymphomas are less likely to cause pancytopenia compared with aggressive lymphomas due to destructive infiltration that affects hematopoiesis in the bone marrow.

The differential diagnosis for hemolysis-associated cytopenias includes microangiopathy hemolytic anemia associated with thrombotic thrombocytopenic purpura, paroxysmal nocturnal hemoglobinuria (PNH), hypersplenism, liver disease, oxidant agents (dapsone), and various infections (viral, bacterial, and parasitic). Laboratory findings consistent with hemolysis include elevated lactate dehydrogenase and reduced haptoglobin levels. The typical presentation of PNH is with hemolytic anemia, hemoglobinuria with subsequent acute renal failure, and hypercoagulable state with venous thrombosis. Paroxysmal nocturnal hemoglobinuria can cause diminished hematopoiesis, resulting in pancytopenia. Hypersplenism can lead to pancytopenia due to trapping of specific cell lines from an increase in phagocytic activity. Portal hypertension can lead to hypersplenism and thus hemolysis in patients with liver disease. Dapsone-induced hemolysis occurs in patients with and without glucose-6-phoshate dehydrogenase deficiency and appears to be dose dependent.

Viral infections, especially HIV, parvovirus B19, EBV, CMV, and hepatotropic viruses (A, B, and C) can also result in pancytopenia. Cytopenias are commonly seen in patients with AIDS. Isolated abnormalities, particularly thrombocytopenia, might be the only laboratory abnormality in the initial presentation of HIV infection. Therefore, HIV should be considered in the assessment of patients presenting with any type of cytopenia. Parvovirus B19 causes erythema infectiosum or arthritis in immunocompetent children and adults, respectively. However, in immunocompromised patients, such as organ transplant recipients, persistent parvovirus B19 infection can lead to pure red blood cell aplasia.[10] Cytopenias are unusual in an uncomplicated CMV infections, but can occur with reactivation disease in immunosuppressed patients, such as those with HIV or transplant recipients. Acute infection with hepatitis A virus might be associated with tran-

sient neutropenia and lymphopenia.[11] Neutropenia can also be seen in chronic hepatitis B or C infection.

Bacterial infections typically associated with cytopenias include typhoid fever, *Shigella enteritis*, brucellosis, and tularemia. Typhoid fever should be suspected in a patient who presents with a febrile illness and abdominal symptoms and reports recent travel to an underdeveloped country or known ingestion of contaminated food or water. Usually, *S enteritis* presents with fever, abdominal cramps, and bloody or mucoid diarrhea. Brucellosis is a zoonotic infection that is typically transmitted by ingestion of unpasteurized dairy products or by contact with fluids from infected animals (sheep, cattle, goats, and pigs). Tularemia is also a zoonotic infection caused *Francisella tularensi* and typically presents with ulceroglandular disease, which includes fever, a single erythematous ulcerative lesion with a central eschar, and tender regional lymphadenopathy.[12]

Rickettsial infections, such as human monocytic ehrlichiosis, human granulocytic anaplasmosis, and Rocky Mountain spotted fever, need to be considered in the differential diagnosis of acute-onset cytopenias as well. Rickettsial diseases have a well-defined geographic distribution that should be considered while entertaining these pathogens in the differential diagnosis. Patients typically present with a febrile illness and have nonspecific symptoms of malaise, myalgia, headache, and chills. Often laboratory findings are significant for leukopenia, thrombocytopenia, and elevated levels of aminotransferases. Anemia might also be seen. Rocky Mountain spotted fever, caused by *Rickettsia rickettsia*, is the most common of the rickettsial diseases.

Parasitic infections, such as kala azar (caused by *Leishmania donovani*) and malaria, are included in the differential diagnosis of pancytopenia in developing countries. Kala azar or "black fever" is the most important clinical manifestation of visceral leishmaniasis and presents with slowly progressive malaise, fevers, weight loss, and splenomegaly. This disease is mostly reported from Mediterranean countries, India, and East Africa.[13]

The list of differential diagnoses in a patient presenting with fevers and pancytopenia is broad. Detailed exposure history and thorough physical examination are critical in selecting the most appropriate tests for expedited diagnosis and appropriate treatment.

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CORRECT ANSWERS: 1. a, 2. c, 3. d, 4. a, 5. e