Aplastic Anemia: Review Questions

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QUESTIONS

Choose the single best answer for each question.

Questions 1 to 4 refer to the following case.

A 20-year-old man presents to the emergency department for evaluation of recurrent epistaxis. He reports a 1-week history of nosebleeds that occur at least once daily and can last up to 45 minutes. Nosebleeds have been progressively worsening. He works in a grocery store and has noticed large bruises on his abdomen and thighs after carrying milk crates. He was able to work up until 2 days ago when he developed fever up to 102°F associated with significant fatigue. The patient denies sinus congestion, throat pain, cough, shortness of breath, nausea, emesis, melena, hematochezia, or hematuria. He also reports headaches and mild gum bleeding when brushing his teeth. On physical examination, vital signs include temperature of 100.8°F, heart rate of 115 bpm, respiratory rate of 22 breaths/min, and blood pressure of 134/75 mm Hg. In general, the patient is pale and fatigued but is in no acute distress. Head, eye, ear, nose, and throat examination reveals that his pupils are equal, round, and reactive to light; extraocular movements are intact; and oropharynx is slightly dry with petechiae on his buccal mucosa and posterior pharynx. He has no sinus tenderness, nuchal rigidity, or neck lymphadenopathy. Heart rate is regular and tachycardic with 2/6 systolic murmur that is loudest at the left lower sternal border. Lungs are clear to auscultation bilaterally. Abdomen has positive bowel sounds and is soft and nontender with no hepatosplenomegaly. The extremities are warm with no edema, but skin examination reveals petechiae present on lower extremities bilaterally. Results of laboratory testing are: white blood cell count of 800 cells/μL, with a differential of 2% neutrophils (segmented), 96% lymphocytes, and 2% monocytes with an absolute neutrophil count (ANC) of 16 cells/μL; hemoglobin, 5.2 g/dL; hematocrit, 14.8%; and platelet count, 5000 cells/μL.

1. **What is the most appropriate next step in the management of this patient?**
   (A) Admit the patient to the hospital for administration of intravenous (IV) antibiotic drugs, blood and platelet transfusions, and a bone marrow biopsy
   (B) Perform blood and platelet transfusion, initiate oral levofloxacin, and draw blood cultures, then arrange for a bone marrow biopsy the next day as an outpatient
   (C) Perform blood and platelet transfusion with follow-up the next day for further evaluation
   (D) Perform bone marrow biopsy the next day as an outpatient

2. **The patient undergoes bone marrow biopsy (Figure). What is this patient's diagnosis?**
   (A) Acute lymphoblastic leukemia
   (B) Acute myelogenous leukemia (AML)
   (C) Aplastic anemia
   (D) Myelodysplastic syndrome (MDS)

3. **What is the most common cause of inherited bone marrow failure?**
   (A) Diamond-Blackfan anemia
   (B) Dyskeratosis congenita
   (C) Fanconi anemia
   (D) Schwackman-Diamond syndrome

4. **The patient undergoes evaluation for bone marrow transplantation. If the patient has a human leukocyte antigen–matched sibling, what is the 5-year survival rate after bone marrow transplantation?**
   (A) 30%
   (B) 50%
   (C) 60%
   (D) 80%

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Questions 5 and 6 refer to the following case.

A 62-year-old man is referred to a hematologist for further work-up of pancytopenia. Two years ago, the patient was diagnosed with chronic lymphocytic leukemia (CLL) and completed 4 courses of fludarabine, cyclophosphamide, and rituximab chemotherapy with excellent response. The patient states that he has had a progressive decline in blood counts within the last 2 months. Physical examination is remarkable for scattered petechiae in his mouth, but no adenopathy or hepatosplenomegaly is noted. Cardiopulmonary examination is normal. Laboratory studies show a white blood cell count of 1300 cells/μL, hematocrit of 25.8%, and platelet count of 12,000 cells/μL. Renal and liver function tests are normal. Bone marrow biopsy reveals a markedly hypocellular marrow with hypocellularity of 10% or less. Flow cytometry shows no evidence of CLL. Cytogenetic studies could not be performed.

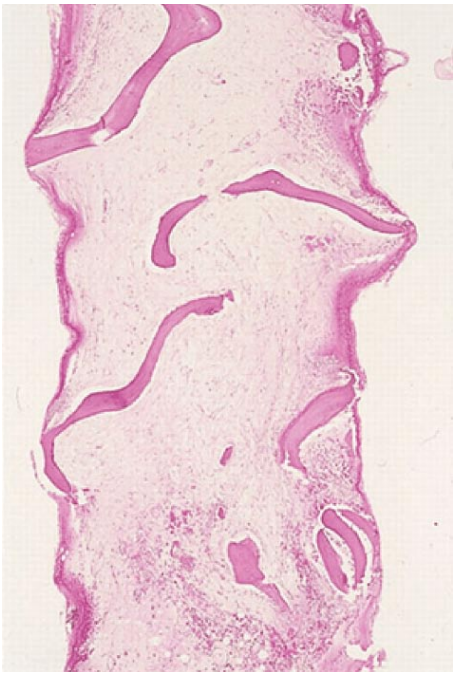

Figure. A bone marrow biopsy of the patient described in questions 1 to 4.

5. How should this patient be treated?

(A) Antithymocyte globulin (ATG) with cyclosporine
(B) Azacitidine in standard doses
(C) Azacitidine with dose reduction
(D) Supportive care alone

6. The patient has a good partial response to the prescribed treatment. Fourteen months after recovery, his blood counts have declined again. What is the most likely cause for this patient's declining blood counts?

(A) CLL
(B) Progressive MDS
(C) Recurrent aplastic anemia
(D) Secondary MDS

ANSWERS AND EXPLANATIONS

1. (A) Admit the patient to the hospital for administration of IV antibiotic drugs, blood and platelet transfusions, and a bone marrow biopsy. This patient requires urgent management of 2 potentially life-threatening conditions. First, he needs inpatient management for neutropenic fever (defined as an ANC < 1000 cells/μL and a temperature ≥ 100.5°F). Patients with neutropenic fever should be hospitalized and given IV antibiotic drugs to cover gram-negative bacteria, particularly *Pseudomonas aeruginosa*. Single-agent empiric antimicrobial agents (eg, cefepime, meropenem/imipenem, piperacillin/tazobactam) can be administered because of their anti-pseudomonal activity. Second, this patient's severe thrombocytopenia requires urgent treatment. Spontaneous bleeding can occur in patients with a platelet count less than 10,000 cells/μL, and patients with mucosal bleeding are at higher risk for severe bleeding. Therefore, a platetet transfusion is required in this case, and given his profound anemia and tachycardia, a blood transfusion should be considered as well. During hospitalization, results of the peripheral smear can be reviewed and red blood cell transfusion and a bone marrow biopsy can be performed. Given this patient's leukopenia, blood products should be irradiated, filtered, and cytomegalovirus-safe to prevent transfusion-associated graft-versus-host disease (GVHD).

2. (C) Aplastic anemia. The bone marrow sample shows no marrow elements and no evidence of dysplasia (Figure). This patient meets criteria for very severe aplastic anemia, with profound neutropenia (ANC < 200 cells/μL), thrombocytopenia (platelet count < 20,000 cells/μL), and marrow cellularity less than 25%. Work-up of aplastic anemia, including viral studies and thorough review of drugs, herbal products, and exposures to chemicals (eg, benzene) and radiation, is necessary. Most cases of aplastic anemia are idiopathic. In idiopathic aplastic anemia, the immune system is thought to cause the destruction of hematopoietic elements. As a result, treatment

options include bone marrow transplantation or immunosuppression. The World Health Organization (WHO) criterion for acute leukemia is a blast count of over 20% in the marrow; this patient's marrow has no evidence of an elevated blast count, making the diagnoses of acute lymphoblastic leukemia and AML unlikely. Also, in acute leukemias, the marrow is usually hypercellular as opposed to hypocellular. Typically, patients with MDS have an elevated cellularity in the bone marrow, and dysplasia is present in more than 1 cell line. However, it is often difficult to distinguish hypocellular MDS from aplastic anemia, particularly in older patients. To consider hypocellular MDS as a diagnosis, cytogenetic abnormalities and/or evidence of dysplasia on the bone marrow specimen should be present.

3. **(C) Fanconi anemia.** The most common cause of inherited bone marrow failure is Fanconi anemia, an autosomal recessive disorder caused by defects in the DNA damage repair pathway. Patients with Fanconi anemia have growth and development anomalies, bone marrow failure and leukemia, and a predisposition to cancers of the aerodigestive tract. The second most common cause of inherited bone marrow failure is dyskeratosis congenita, a disease characterized by bone marrow failure, oral leukoplakia, pigmentation changes in the skin, and nail dystrophy. Multiple genetic mutations are associated with dyskeratosis congenita, but they all cause defects in telomere maintenance. In Diamond-Blackfan anemia, progression to MDS or aplastic anemia can occur, but Diamond-Blackfan anemia is typically characterized by pure red blood cell aplasia. Schwackman-Diamond syndrome is characterized by pancreatic exocrine dysfunction, neutropenia, and metaphyseal dysostosis, but progression to aplastic anemia, MDS, and AML is not uncommon. Diamond-Blackfan anemia and Schwackman-Diamond syndrome appear to stem from defective ribosomal RNA processing. It is important to identify whether bone marrow failure is related to an inherited disorder because the choice of treatment and subsequent patient outcomes will be affected.[1]

4. **(D) 80%.** Matched-sibling allogeneic bone marrow transplants in young patients with aplastic anemia have an excellent outcome, with survival rates approaching 90% with current supportive care.[2–4] The quality of life for these patients is outstanding as well. Aplastic anemia is the only indication for urgent bone marrow transplantation when a fully matched relative is identified. GVHD is a significant concern and influences outcomes after transplantation. For this reason, the focus of current research is reducing the incidence of GVHD in patients undergoing bone marrow transplantation.

5. **(A) ATG with cyclosporine.** This patient's hypocellular bone marrow and declining blood counts are consistent with aplastic anemia. Some studies describe marrow aplasia after treatment with fludarabine and cyclophosphamide, but the cause is unclear. A possible link between T-cell suppression and emergence of autoreactive lymphocytes has been suggested. Given the patient's age, first-line therapy would be a combination of cyclosporine and ATG. Overall response rate with this therapy is 50% to 60%.[2,5] Azacitidine is used to treat MDS, not aplastic anemia. Supportive care alone is not recommended for patients with aplastic anemia, as outcomes are extremely poor.

6. **(C) Recurrent aplastic anemia.** Relapsed aplastic anemia occurs in approximately 30% of patients treated with ATG and cyclosporine.[5] One variable that affects rates of relapse is the taper schedule for cyclosporine, with relapse rates much higher in patients who undergo a rapid taper schedule. Many relapses can be treated effectively with reinstitution of immunosuppression. If a patient fails to respond to immunosuppressive therapy, bone marrow transplantation must be considered. Another important consideration in this case is secondary MDS. Up to 20% of patients with aplastic anemia treated with immunosuppression will develop secondary clonal hematopoietic diseases, including MDS, acute leukemia, and paroxysmal nocturnal hemoglobinuria. Repeating the bone marrow biopsy to rule out a secondary clonal disorder is appropriate in this case. A bone marrow biopsy would also rule out both progressive MDS and CLL, which are considerations in this case but are less likely overall.

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