HEMATOLOGY BOARD REVIEW MANUAL

Autoimmune Hemolytic Anemia

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QUESTIONS

1. You are called to consult on a patient with end-stage liver disease and anemia. His hematocrit is 25%. He is noted to have a direct antibody test (DAT) that is positive for IgG antibodies but negative for C3. He has a normal lactate dehydrogenase (LDH) level at 185 U/L and a normal reticulocyte count. What is the next step in the management of this patient?
   A. Consult surgery about splenectomy
   B. Order measurement of ferritin level and additional laboratory tests plus review blood smear looking for other causes of anemia
   C. Start mycophenolate 500 to 1000 mg twice daily
   D. Start prednisone at 1 mg/kg/day
   E. Start rituximab at 375 mg/m² weekly × 4 weeks

2. A 78-year-old woman who has developed severe anemia but is otherwise healthy presents for evaluation. Her past history is unremarkable. Physical exam reveals shotty nodes but is otherwise normal. Laboratory testing shows a hematocrit of 19%, an elevated LDH concentration that is twice the upper limit of normal, and a reticulocyte count (corrected) of 3%. Her DAT is negative for IgG but positive for C3. What is the treatment of choice for her hemolysis?
   A. Danazol 200 mg 4 times daily
   B. Intravenous immunoglobulin 1 g/kg
   C. Prednisone 1 mg/kg daily
   D. Rituximab at 375 mg/m² weekly × 4 weeks
   E. Splenectomy

3. A 37-year-old man who was diagnosed with warm AIHA several months ago presents for a follow-up visit. He responded to prednisone therapy but cannot be weaned off steroid therapy as his hemolysis flares whenever his dose is decreased under 20 mg per day. He has also developed diabetes and had a flare of his chronic hepatitis B when he first started high-dose steroids. He is otherwise healthy. What is the next most reasonable option for therapy?
   A. Cyclophosphamide 1000 mg IV every 28 days
   B. Danazol 200 mg 4 times daily
   C. Fludarabine 40 mg/m² orally days 1–5, 29–34, 57–61, and 85–89
   D. Rituximab at 375 mg/m² weekly × 4 weeks
   E. Splenectomy

4. You are called to consult on a critically ill patient in the intensive care unit. She had an uncomplicated hysterectomy 2 weeks ago but presented today gravely ill with severe hypotension. Her hematocrit is 12% with signs of hemolysis and a positive DAT. She also has renal failure and florid disseminated intravascular coagulation (DIC). Which of the following drugs is most likely to cause the type of reaction observed in this patient?
   A. Cefotetan
   B. Fludarabine
   C. Methylprednisolone
   D. Penicillin
   E. Trimethoprim/sulfamethoxazole

5. You are asked to consult on a 46-year-old man with “bicytopenia.” Review of the patient’s laboratory test results shows his platelet count is only 5000/µL. The hematocrit is 20% with a corrected reticulocyte count of 10%, and the LDH concentration is elevated 3 times the upper limit of normal. Examination reveals a large spleen and shotty nodes. After 1 week of prednisone therapy at 1 mg/kg daily, there is a rise in both the hematocrit and platelet count. What is the most likely underlying disorder in this patient?
   A. Autoimmune lymphoproliferative disease
   B. Hemolysis due to dapsone therapy
   C. Marginal zone lymphoma
   D. Mycoplasma infection
   E. Peripheral T-cell lymphoma

ANSWERS

1. The correct answer is (B), Order measurement of ferritin level and additional laboratory tests plus review blood smear looking for other causes.
of anemia. This patient most likely has a false-positive DAT due to his liver disease. His normal LDH level is strong evidence against hemolysis as the LDH is a very sensitive screen for the presence of hemolysis. Prednisone would be a reasonable first step if the patient were diagnosed with warm autoimmune hemolytic anemia (AIHA). Splenectomy and rituximab are reserved for patients with warm AIHA in whom steroid therapy fails. Mycophenolate is reserved for patients refractory to several lines of therapy.

Reference

2. The correct answer is (D), **Rituximab at 375 mg/m² weekly × 4 weeks.** The patient’s DAT is positive for C3 and not IgG, indicating that she has cold antibody disease. Steroids are not effective in cold antibody disease. Since most C3-coated red cells are destroyed in the liver, splenectomy also would not be effective. Rituximab appears to have the highest response rate and should be started early in symptomatic patients with cold AIHA. Danazol is used to treat warm antibody disease that has not responded to initial therapy such as rituximab or steroids.

Reference

3. The correct answer is (E), **Splenectomy.** Splenectomy would be the next step, as it has a reported response rate ranging from 50% to 80%, with 50% to 60% of patients remaining in remission. Rituximab also has a high response rate in warm AIHA, but it is contraindicated in patients who are chronic carriers of hepatitis B virus. Danazol is a third-line agent and would not be a good choice in this patient due to concerns about liver toxicity. Cyclophosphamide is also a third-line agent, and most experience with fludarabine has been in cold AIHA.

References

4. The correct answer is (A), **Cefotetan.** Cefotetan has been associated with a fulminant AIHA that is accompanied by severe DIC and is often fatal. Exposure to cefotetan often occurs during surgery when the drug is given for antimicrobial prophylaxis. While fludarabine and methyldopa most often initiate a warm AIHA, the clinical course is typical and not as fulminant as this patient’s course; penicillin coats the red cells, resulting in a positive DAT but rarely clinical hemolysis. Trimethoprim/sulfamethoxazole can lead to hemolysis via an immune complex mechanism and can result in clinical hemolysis, but not hemolysis with DIC.

Reference

5. The correct answer is (E), **Peripheral T-cell lymphoma.** The occurrence of hemolysis and thrombocytopenia together with each responsive to steroids is highly suggestive of immune etiologies for both. In adults with Evans syndrome (AIHA plus idiopathic thrombocytopenic purpura), one needs to be concerned with T-cell lymphomas. Autoimmune lymphoproliferative disease can present as Evans syndrome, but this most often occurs in children. Marginal zone lymphoma is associated with chronic cold AIHA, while Mycoplasma infections are associated with acute cold AIHA. Dapsone leads to hemolysis via oxidation of hemoglobin.

Reference