Residents’ Clinic

68-Year-Old Man With Anemia and Renal Failure

HORNG H. CHEN, M.D.,* RAYMOND C. SHIELDS, M.D.,* AND WILLIAM T. BARDSTY, M.D.†

A 68-year-old man went to a local emergency department because of midabdominal, dull, postprandial pain that had persisted for 3 hours, preceded by nausea. He had a history of hypertension, coronary artery disease, and aortic stenosis. He had undergone two-vessel coronary artery bypass grafting and St. Jude aortic valve replacement 3 years earlier, followed by long-term coumarin therapy. He also had a 50-pack-year history of smoking. His vital signs on admission to the local hospital were as follows: blood pressure, 159/73 mm Hg; pulse rate, 72 beats/min; respirations, 16/min; and temperature, 36.7°C. Findings on physical examination were unremarkable except for mild tenderness over the epigastrium on deep palpation. The patient had no rebound tenderness. Bowel sounds were present, and no masses were palpated. Rectal examination disclosed no notable findings. Laboratory investigations revealed the following: hemoglobin, 7.7 g/dL (normal, 13.5 to 17.5); hematocrit, 21.0% (normal, 38.8 to 50.0%); mean corpuscular volume, 89.5 fl (normal, 81.2 to 95.1); leukocyte count, 6.7 x 10⁹/L (normal, 3.5 to 10.5 x 10⁹); platelet count, 151 x 10⁹/L (normal, 150 to 450 x 10⁹); prothrombin time, 21.5 seconds (normal, 8.4 to 12.0); international normalized ratio (INR), 2.8; creatinine, 4.1 mg/dL (normal, 0.8 to 1.2); blood urea nitrogen, 62 mg/dL (normal, 10 to 38); lactate dehydrogenase (LDH), 240 U/L (normal, 112 to 257); amylase, 48 U/L (normal, 35 to 115); total bilirubin, 1.0 mg/dL (normal, 0.1 to 1.1); alkaline phosphatase (ALKP), 138 U/L (normal, 98 to 251); aspartate aminotransferase (AST), 51 U/L (normal, 12 to 31); and haptoglobin, 215 mg/dL (normal, 40 to 300). Two years previously, hemoglobin and creatinine levels were 13.0 g/dL and 1.4 mg/dL, respectively.

1. Which one of the following is the least likely cause of this patient’s anemia?
   a. Ruptured abdominal aortic aneurysm
   b. Cancer of the colon
   c. Peptic ulcer disease
   d. Hemolysis caused by the prosthetic aortic valve
   e. Renal failure

With a history of cigarette smoking and atherosclerotic disease, this patient has an increased risk for development of an abdominal aortic aneurysm (AAA). Acute aneurysm ruptures that are usually contained in the retroperitoneum can manifest with anemia and occasionally with common bile duct obstruction. Cancer of the large bowel frequently occurs in this age-group and can manifest with insidious blood loss. Abdominal pain (particularly epigastric) is a common symptom in peptic ulcer disease, which is often complicated by hemorrhage, especially in the presence of long-term anticoagulation. Prosthetic valve-associated hemolysis is the least likely cause of anemia in this patient because of lack of evidence of hemolysis, as indicated by normal LDH, bilirubin, and haptoglobin levels. Clinically significant hemolysis associated with a mechanical valve prosthesis is rare in the absence of perivalvular leak. Hemolytic anemia occurs more commonly in prosthetic mitral valve recipients than in aortic valve recipients and is associated with a decreased level of serum haptoglobin. Anemia attributable to lack of erythropoietin production in renal failure should be considered a possibility in view of the patient’s long history of hypertension.

The patient received a transfusion of 6 units of packed erythrocytes, which resulted in a hemoglobin level of 11.9 g/dL. He underwent upper gastrointestinal endoscopy and colonoscopy, neither of which disclosed the cause of anemia. The cause of his anemia remained uncertain. Abdominal ultrasonography showed multiple gallstones and a slightly thickened gallbladder wall, normal hepatic bile duct diameter, and an AAA 4.7 cm in diameter. The patient was transferred to our medical center for further evaluation.

On examination, the patient had stable vital signs, no fever, and a nontender abdomen. Laboratory evaluation at the time of admission revealed the following: hemoglobin, 11.2 g/dL; leukocyte count, 7.2 x 10⁹/L; platelet count, 126 x 10⁹/L; prothrombin time, 18.3 seconds; INR, 1.8; creatinine, 3.2 mg/dL; urea, 80 mg/dL; AST, 168 U/L; ALKP, 305 U/L; alanine aminotransferase, 236 U/L (normal, 10 to 45); LDH, 300 U/L; total bilirubin, 3.5 mg/dL; direct bilirubin, 0.6 mg/dL (normal, 0.0 to 0.3); and amylase, 40 U/L. Chest roentgenographic findings were normal. A computed tomographic (CT) scan of the abdomen revealed an infrarenal aortic aneurysm that was 4.5 cm in diameter without evidence of rupture. Bilateral small renal calculi, bilateral renal masses consistent with simple cysts, and hemorrhage were also noted. On the day after admission, gross hematuria developed. On further questioning, the patient reported a 2-
A 68-year-old patient with asymptomatic hematuria, a urinary tract neoplasm, half of which are malignant. In our 68-year-old patient with asymptomatic hematuria, a urinary tract neoplasm as well as benign prostatic hypertrophy is the primary consideration. Renal artery embolism must be considered in any patient with hematuria who has the classic risk factor of valvular heart disease or cardiac arrhythmia. A major noncardiac source of renal emboli is ruptured aortic atheromatous plaque. Although our patient had a prosthetic heart valve and was receiving oral anticoagulant therapy, the occurrence of renal artery embolism is not precluded; cases of cholesterol embolization precipitated by oral anticoagulants have been reported. Renal artery embolism is rare, and diagnosis necessitates a high index of suspicion because of its varied clinical manifestations—nausea, vomiting, persistent flank pain, or, commonly, no symptoms. Glomerulonephritis in patients older than 40 years rarely is associated with gross hematuria. The most common glomerular disease associated with asymptomatic gross hematuria is IgA nephropathy. Genitourinary findings seldom are an isolated manifestation of tuberculosis. Pulmonary disease is usually present, and the clinical features are subacute to chronic, rather than acute as in our patient. Usual associated findings are cystitis and sterile pyuria instead of hematuria.

On cystoscopy, our patient was found to have an enlarged prostate with bleeding vessels, which were fulgurated successfully. No other pathologic process was noted in the urinary bladder. Mild hematuria persisted despite fulguration, and the cause of his intermittent hematuria was unclear. We elected to observe that symptom and assess his renal function, with the thought that the hematuria and renal failure might have a common cause.

**3. Which one of the following is least likely to have contributed to the renal insufficiency in our patient?**

   a. Atheroembolic disease of the renal artery
   b. Renal malignant lesion
   c. Glomerulonephritis
   d. Hypertensive nephrosclerosis
   e. Hydronephrosis

Typically, atheroembolic disease results from multiple showers of cholesterol-containing microemboli dislodged from atheromatous plaques in large arteries. With an AAA, our patient is at risk for this complication. Most episodes of atheroembolism occur spontaneously, but they are frequently seen after manipulation of the vessels, such as for aortic surgical procedures or arteriography, and commonly involve other organs, such as the retina, skin (livedo reticularis), muscle, and brain. Our patient had no clinical features of embolic involvement of other organs. A renal malignant lesion can cause renal failure by three mechanisms: direct infiltration of the renal parenchyma, immune factors, and postrenal obstruction due to direct compression by the tumor or enlarged lymph nodes. In our patient, a CT scan of the abdomen revealed bilateral renal masses. With the presence of hematuria, a renal malignant tumor must be considered a potential cause of the renal failure. Because of the presence of hematuria and proteinuria, glomerulonephritis should also be considered. Arterial nephrosclerosis—the progressive obliteration of the renal vascular bed—occurs in patients with hypertension and accounts for 15 to 30% of new dialysis cases. Our patient had a 20-year history of hypertension that could contribute to the renal insufficiency, even though it is unlikely to be the only cause of the severe decline in renal function from a creatinine level of 1.4 to 4.1 mg/dL during a period of 2 years. Hydronephrosis-induced renal failure would imply chronic bilateral involvement of the kidneys, which would be easily detected on ultrasound studies or CT scans of the abdomen. In our patient, however, both ultrasonography and CT scans of the abdomen were negative for hydronephrosis.

On further evaluation, the erythrocyte sedimentation rate was 38 mm in 1 hour (normal, 0 to 22), rheumatoid factor was 243 IU/mL (normal, 0 to 39), and tests for antiglomerular basement membrane antibody and antineutrophilic cytoplasmic antibody were negative. Because of the numerous inconclusive results, we decided to do an ultrasound-guided renal biopsy to obtain a definitive diagnosis. The oral coumarin therapy was discontinued, and intravenous administration of heparin was initiated before the renal biopsy was performed. An ultrasound-guided biopsy of his left kidney revealed evidence of IgA nephropathy and a small cell malignant lymphoma of B-cell origin. Bone marrow aspiration also showed lymphomatous involvement.
4. **In the context of the histologic findings from the renal biopsy in our patient, which one of the following statements is true?**
   a. A direct association exists between IgA nephropathy and chronic lymphocytic leukemia and B-cell lymphoma
   b. IgA nephropathy is a benign disease
   c. Serum total IgA is increased in 90% of adults with IgA nephropathy
   d. Lymphomatous infiltration of the renal parenchyma is a common cause of renal failure in patients with lymphoma
   e. Primary renal lymphoma is a rare occurrence

IgA nephropathy has been sporadically associated with non-Hodgkin’s lymphoma, mixed cryoglobulinemia, polycythemia, and other diseases. These associations, however, have been random. In about 30% of patients with IgA nephropathy, end-stage renal failure develops within 20 years after diagnosis. Serum total IgA is increased in 33 to 50% of adults with IgA nephropathy. Serial determinations have not been correlated with the severity or activity of the disease. Therefore, this determination is not useful in diagnosing or following the course of IgA nephropathy. Lymphomatous infiltration of the kidneys rarely causes renal failure. Primary renal lymphoma is rare; some investigators are skeptical that it occurs.

In our patient, coumarin therapy was resumed 3 days after the renal biopsy. Approximately 2 days later, he noted acute left flank pain. The prothrombin time and INR were 20.2 seconds and 2.1, respectively. An emergency abdominal CT scan revealed a large hematoma in the left perinephric area.

Our patient demonstrated the practical problems in the day-to-day management of patients with prosthetic heart valves. We were concerned about the optimal anticoagulation, the risk of bleeding, and the risk of interrupting anticoagulation if our patient were to undergo surgical treatment.

5. **Which one of the following statements is false regarding the risk of thromboembolism as it relates to St. Jude aortic valve placement in our patient?**
   a. The risk in our patient decreases by almost twofold in contrast to patients with mitral valve prosthesis
   b. Our patient has a higher risk than do patients with caged-ball cardiac valves
   c. The ideal intensity of anticoagulation for our patient is an INR between 2.5 and 3.5
   d. Antiplatelet therapy alone is not recommended for prevention of thromboembolism in our patient
   e. The St. Jude valve is associated with the lowest incidence of thromboembolism

A publication that summarized studies performed between 1970 and 1992 on embolic or bleeding complications in patients with mechanical valve prostheses reported the following conclusions: (1) the incidence of major embolism in the absence of antithrombotic therapy was 4 per 100 patient-years; (2) with antiplatelet therapy, the risk was reduced to 2.2 per 100 patient-years; (3) with coumarin therapy, the risk of embolic or bleeding complications was reduced to 1 per 100 patient-years; (4) a mitral prosthesis increased the risk of major embolism by almost twice that for an aortic prosthesis; (5) tilting-disk valves and bileaflet valves (for example, St. Jude) showed a lower incidence of major embolism in comparison with caged-ball valves; and (6) the incidence of major bleeding in patients treated with coumarin was 1.4 per 100 patient-years. The recommended therapeutic range of anticoagulation is an INR of 2.5 to 3.5 for “routine-risk” patients (not those with first-generation mechanical valves, caged-ball valves, caged-disk valves, and other risk factors for thromboembolism such as atrial fibrillation). Antiplatelet therapy, in addition to oral anticoagulation, provides further protection but increases the risk of bleeding (especially with aspirin). Antiplatelet therapy alone, however, does not consistently protect patients with mechanical prosthetic heart valves, including patients in sinus rhythm with an aortic St. Jude valve. St. Jude valve is associated with the lowest incidence of thromboembolism, and for patients with uncomplicated St. Jude aortic valve replacement, an INR of 2.0 to 2.8 is suggested for thromboembolic prophylaxis.

Our patient did well with conservative management of the perinephric hematoma. His hemoglobin level decreased to 7.6 g/dL, and he was given 2 units of packed erythrocytes. Anticoagulant therapy was withheld, and the hemodynamic status was closely monitored; however, the creatinine level increased from 3.5 to 4.7 mg/dL. Because of his poor renal function, we decided to treat his lymphoma with prednisone, 80 mg/day orally. At 2 months, renal function had improved, and the creatinine level was 2.0 mg/dL. The AAA was considered asymptomatic without signs of hemorrhage; follow-up was scheduled for every 6 months. Because of the prosthetic valve, the risks of thromboembolism were again discussed with the patient. Continued use of low-dose coumarin, with a target INR of 2.0, was recommended.

**DISCUSSION**

This complex case demonstrates the need to consider multiple uncommon disease processes in the evaluation of common initial manifestations. The underlying medical problems (presence of AAA, renal calculi, history of heart valve replacement, and long-term anticoagulation) unrelated to the final diagnosis also prompted the consideration of various diagnoses. Thus, the numerous issues encountered did not initially suggest a single diagnosis. This case also emphasizes the need to investigate the most common factors contributing to the initial symptoms while remembering the less
common but equally consequential diagnoses. The acute life-threatening conditions had to be excluded before other diagnostic possibilities could be considered. Our patient initially had postprandial abdominal pain. Routine blood tests revealed anemia and renal insufficiency, both of which warranted further evaluation. Demonstration of multiple gallstones on abdominal ultrasonography made biliary colic the most likely cause of the abdominal pain. Because of the complicated hospital course, spontaneous resolution of the pain, and normalization of results of liver function tests, surgical intervention was not recommended.

The clinical manifestations did not seem to be due to rupture of the AAA. Management of asymptomatic 4- to 5-cm AAAs is controversial. In general, expansion of the aneurysm more than 0.5 cm during a 6-month period or development of symptoms warrants prompt reevaluation for elective surgical repair. Therefore, our patient should undergo reassessment at least every 6 months. The high-risk medical conditions for operative AAA repair include (1) severe coronary or valvular heart disease, (2) decompensated chronic obstructive pulmonary disease, (3) chronic renal failure, (4) hepatic cirrhosis in conjunction with portal hypertension, and (5) chronic hematologic disorders associated with bleeding dyscrasias. Of these factors, renal failure poses the greatest operative risk to our patient and the risk is highest when serum creatinine levels exceed 3 mg/dL.

In our patient, the potential causes of hematuria included anticoagulant therapy, prostatic hypertrophy, and IgA nephropathy. In IgA nephropathy, 40 to 50% of the patients have macroscopic hematuria. Periodic gross hematuria is common in men with benign prostatic hypertrophy. As the prostate enlarges, the blood vessels in the mucosa tend to become numerous and fragile and thus more susceptible to bleeding. The extent of contribution of any of these entities in the development of hematuria in our patient is uncertain.

The renal failure in our patient was likely a combined result of IgA nephropathy, lymphoma, and hypertension. Renal complications of lymphoma can originate through the following mechanisms: a direct consequence of the tumor, such as metastatic invasion of the parenchyma or hydro-nephrosis; hypercalcemic nephropathy; an immunologic reaction, such as nephrotic syndrome; or a complication of therapy, such as radiation-induced nephritis. Even though lymphomatous infiltration of the kidneys rarely causes renal failure, we believe that it contributed to the renal failure in our patient because his creatinine level decreased after 2 months of prednisone therapy. Although corticosteroid therapy may reduce proteinuria in patients with IgA nephropathy, it does not improve renal function. The overall outlook for our patient’s renal function is poor because, in patients with IgA nephropathy, hypertension and proteinuria portend a poor prognosis.

The role of anticoagulation in our patient deserves discussion. The optimal intensity of oral anticoagulation is that at which the incidences of thromboembolic and bleeding complications are lowest. Investigators have suggested that the intensity of anticoagulation should be adjusted on the basis of type and position of the cardiac valve. That study also demonstrated that the higher thromboembolic risk with caged-ball and tilting-disk valves can be substantially reduced by anticoagulation with an INR of 4.0 to 4.9. Patients with bileaflet valves, such as in our patient, apparently derive no additional benefit when the INR exceeds 3.0. The risk of adverse events (primarily hemorrhage) increases sharply with an INR greater than 5.0. That study also presented the concept of target INR range, 3.0 to 4.0—a smaller range within the optimal INR range of 2.5 to 4.9. Therefore, by aiming for the target INR within the optimal range, the risk of overanticoagulation or underanticoagulation can be reduced. Until more data are available, however, the recommendations from the American College of Chest Physicians remain the standard guidelines for anticoagulant therapy, with the additional stipulation that the intensity of anticoagulation be maintained at the upper end of the recommended range.

REFERENCES
5. Hypertension Detection and Follow-Up Program Cooperative Group. Five-year findings of the Hypertension and Follow-Up Program. I. Reduction in mortality of persons with high blood pressure, including mild hypertension. JAMA 1979; 242:2562-2571

Correct answers: 1. d, 2. b, 3. e, 4. e, 5. b