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Hematuria Status Post Renal Biopsy

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Hematuria Status-post Renal Biopsy

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This is a case of a 66 year old Caucasian woman admitted to the hospital following a ureteroscopic biopsy of the left renal pelvis. The biopsy was performed for asymptomatic hematuria, with a retrograde intravenous pyelogram revealing a mass in the left renal pelvis. The patient developed lightheadedness and left flank pain 12-24 hours following the procedure and was found to have a 3 gram drop in hemoglobin compared to blood work performed during the previous week.

One week prior to the biopsy, the following lab studies were done: hemoglobin 10.4 gm/dL, platelets 230,000/mL3, creatinine 1.0 mg/dL, prothrombin time (PTT) 41 seconds (25-35), and protime (PT) 12 seconds (11-13). On admission, a CT scan was performed which showed a large left subcapsular renal hematoma with blood in the peritoneal space. Repeat labs at the time of admission were: hemoglobin 7.4 mg/dL, platelets 311,000/mL^3, creatinine 3.4 mg/dL, PTT was 46 seconds, PT 13 seconds. She was transferred to the intensive care unit and stabilized with intraveinous fluids and blood products.

Her past medical history included hypertension, hypothyroidism, post-operative deep vein thrombosis (15 yrs ago), and recent hematuria. Her past surgical history included hip replacement, which was not complicated by bleeding diathesis. Her social history was not significant for any alcohol or tobacco use. Medications included levothyroxine and amlodipine, which she had been taking for some time. She denied the use of over the counter products, such as aspirin or ibuprofen. There was no family history of bleeding disorders.

Physical exam at the time of admission to the intensive care unit revealed a temperature of 99 degrees Fahrenheit, heart rate of 92, blood pressure of 104/80 mm/Hg (following fluids), and SaO2 of 93% on room air. Pertinent positive findings included bibasilar crackles, and left flank tenderness without any rebound or guarding. Pertinent negatives included no skin lesions or ecchymoses.

On the day of admission to the intensive care unit, the patient underwent an arteriogram, which localized the site of bleeding to the biopsy site. During the arteriogram, multiple coils were inserted in the vicinity of the bleed, but hemostasis was unable to be achieved. Within the first 24 hours, 16 units of fresh frozen plasma were given without achieving hemostasis, and 2-4 units of packed red blood cells were needed to maintain a stable hemoglobin. Two days into admission, she underwent a procedure to embolize the vascular supply to the region where the bleeding was originating from. Transfusion requirements and the degree of hematuria were decreased, however, in the groin, oozing was still present at the site of arteriogram catheter insertion.

Discussion

The patient underwent a routine procedure that can be complicated by hematuria, however, hematuria to this degree is extremely rare. During the ureteroscopic procedure, no discrete mass could be identified. Biopsies were taken in the region that the abnormality was noted on intravenous pyelogram. Transitional cell carcinoma comprises 90% of malignancies in this region and does not have a propensity for bleeding, however, renal cell and metastatic melenoma can occur and both are very vascular tumors. The diagnostic test of choice for renal cell carcinoma is CT with contrast. This was performed during the initial work up one to two months prior to the biopsy with no masses noted. In the majority of cases, it would be expected to find a skin lesion or a history of a lesion in the past if metastatic melenoma was suspected in the differential. No lesions were noted.

Platelet disorders may also cause a persistent bleed. In this case, both pre-biopsy and post-biopsy platelet count were within normal limits. The possibility of a qualitative platelet dysfunction remained. The most common cause is drugs a list of which includes non-steroidal anti-inflammatory drugs, penicillins, cephalosporins, and heparin. Alcohol also has a strong effect on platelet function. The patient denied use of any of these. Uremia also decreases platelet function, and she presented with an elevated creatinine on admission. Her acute renal failure, however, was likely the result of a combination of direct nephron damage from bleeding in addition to hemodynamic instability. The patient's renal function gradually improved throughout hospitalization.

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Coagulopathy, like platelet dysfunction, can also lead to this degree of bleeding. On pre-operative labs it was noted that her PTT was slightly elevated. PTT is used to monitor heparin therapy and screen for abnormalities in the factors of the intrinsic pathway. It is a measure of all the blood factors except Factor VII. The PT is used to evaluate the extrinsic pathway and becomes prolonged when factors drop below 50% of their normal range. Emphasis must be placed on the fact that an abnormal PTT needs immediate attention. One second over normal represents a concentration of one of the intrinsic factors less than 25%. The hematology consult group evaluated the patient and suspected that the bleeding diathesis was related to the abnormal PTT. Appropriate measures were taken for both the treatment and diagnosis.

When evaluating a patient that presents with a prolonged PTT, it is important to first review the medication list for medications such as heparin. The next step is to perform a mixing study. In a mixing study, the patient's blood is mixed with an equal amount of blood from a donor with normal partial PTT. After mixing, the PTT is rechecked, and if it has corrected to within the normal range, then an intrinsic factor deficiency is present. If the PTT does not normalize, then a factor inhibitor or lupus anticoagulant are the most likely etiology. The mixing study in this patient did not correct (PTT=41) and it was strongly suspected that the patient possessed an inhibitor to an intrinsic factor.

From a diagnostic standpoint, the work up centered on determination of which factor was inhibited, and to what degree. Factor VIII inhibitors are by far the most common acquired inhibitors, with an incidence of about one per million annually. Patients usually present after fifty years of age. The autoantibodies are IgG molecules that are directed against the A2 or C2 domains of the Factor VIII molecule. The patient's Factor VIII level was 0.02 (0.46-1.5) and Factor VIII antibody level was 21.7 (<0.6). Factor IX and XI deficiencies may also present like this. These factor levels were normal in this case.

Clinical manifestations of a Factor VIII inhibitor are primarily bleeding into skin or muscle, but bleeding can occur at any site. More than 80% of individuals have one or more episodes of major bleeding. As in this case, the hallmark of a Factor VIII inhibitor is the prolongation of the PTT with a normal PT. This pattern also occurs with factor deficiencies, but as previously mentioned, the mixing study is used to differentiate the two conditions. When normal plasma is mixed with plasma containing an inhibitor, the PTT remains prolonged. A repeated PTT one to two hours after the plasma is mixed is essential because weak inhibitors require time to inactivate the factor. The mixing study suggested an inhibitor, and the next step was to perform the Bethesda assay. The Bethesda assay establishes the diagnosis and gives quantitative information. One Bethesda Unit (BU) is defined as the reciprocal of the patient plasma dilution that creates a 50% residual Factor VIII activity in the test system. This assay tends to underestimate the effect of the inhibitor.

Management of these patients entails both control of acute bleeding and elimination of inhibitor to Factor VIII. Therapy to control bleeding is based on the titer of the inhibitor. For example, with low-titer inhibitors (<5 BU) use of DDAVP or human Factor VIII may control bleeding. High-titer inhibitors (>5 BU) require porcine Factor VIII or recombinant Factor VIIa. The patient had an inhibitor level of 21.7 BU and recombinant Factor VIIa was started. Factor VIIa is given in a dose of 90 ug/kg IV every two to three hours. The factor binds to tissue factor at sites of injury activating Factor X, which results in local thrombin formation. The duration of treatment is variable and based on clinical improvement. With our patient, signs of bleeding abated almost instantaneously when Factor VIIa infusion was begun. She required approximately 3 days of treatment. The other course of treatment, which was not used in this case, is porcine Factor VIII. Most inhibitors cross-react minimally with porcine factor as compared to exogenous human Factor VIII. When a Factor VIII inhibitor is suspected, an inhibitor level to porcine Factor VIII is sent with other labs which measure the factor level and antibody titer. This patient had a porcine Factor VIII antibody level less than 0.6 (<0.6).

The recommendations regarding long term management are anecdotal and often unsuccessful. The factors that predispose to formation of these inhibitors are unknown, and

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in one-third of the cases the inhibitors will spontaneously disappear. Typically, prednisone is the initial agent used to eradicate the inhibitor. Responders generally have higher factor levels and lower inhibitor levels at presentation. If prednisone is not effective, then a trial of chemotherapy is warranted. Commonly used agents include cyclophosphamide, azathioprine, and cyclosporine.

As previously mentioned, the etiology of inhibitor formation is unclear, but there are certain conditions with which it is associated. Hemophilia is by far the most common predisposing condition. Systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and malignancies are also frequently associated with the presence of inhibitors. No clinical or laboratory signs were noted for SLE or RA in the above patient. She presented with acute renal failure and a twenty-four hour creatinine and protein were sent. Results revealed proteinuria with 1.8 grams of lambda light chain. Serum protein electrophoresis (SPEP) also revealed a lambda light chain spike. Bone marrow biopsy revealed 20% plasma cells and serum gamma globulins were decreased. With this information, criteria were met for the diagnosis of multiple myeloma. An association between multiple myeloma and Factor VIII inhibitor has been noted, but is extremely rare.

This patient had a Factor VIII inhibitor, likely caused by the multiple myeloma. This case emphasizes the need to approach the bleeding patient with a broad differential. One of the most common initial presentations of patients with factor inhibitors is persistent bleeding following a minor surgical procedure. This patient also had an elevated PTT on pre-operative labs, which indicated a factor level less than 25% of one of the intrinsic factors. Whenever an unexplained elevation of the PTT is noted, a mixing study must be performed. The mixing study will differentiate between a factor deficiency versus factor inhibitor. As a general internist, emphasis must be placed on early suspicion of these types of cases followed by initiation of a proper work up.

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