91-Year-Old Man With Upper Extremity Ecchymoses

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A 91-year-old man with a medical history significant for previous ischemic stroke, tuberculosis status post lung resection, and type 2 diabetes mellitus presented to his primary care physician with extensive non-traumatic bruising of the bilateral upper extremities.

Approximately 6 weeks earlier, the patient developed diffuse pruritus of the upper extremities, resulting in multiple excoriations, which were subsequently controlled with antihistamine medication. After the initial excoriations, he began to develop associated bruising and swelling of the bilateral upper extremities, which became progressively painful over time. Of note, he was not receiving any antiplatelet or anticoagulant therapy and reported no recent use of nonsteroidal anti-inflammatory medications; prescribed medications included glibenpiride, insulin, metformin, famotidine, simvastatin, triamcinolone, timolol, and latanoprost.

A review of systems was unremarkable aside from the bruising and a 1-week history of severe fatigue impairing normal daily activities. He denied epistaxis, gum bleeding, new joint pain/swelling, hemoptysis, hematuria, and melena. He also denied a history of excessive bleeding after dental work or surgical procedures. Age-appropriate cancer screening was up to date and normal.

On physical examination, the patient was found to have a grade 1/6, systolic, soft, mid-peaking murmur, loudest at the right upper sternal border without radiation. The lungs were clear to auscultation bilaterally without ronchi, wheezes, or rubs. The patient’s abdomen was nontended and nontender with positive bowel sounds and no evidence of organomegaly. The bilateral upper extremities were ecchymotic and tender, with induration distal to the elbows without other physical evidence of active bleeding. Initial laboratory testing revealed a normocytic anemia with a 2 g/dL decrease in a previously stable hemoglobin level to 10.8 g/dL (normal range, 13.5 to 17.5 g/dL), a normal platelet count, a prolonged activated partial thromboplastin time (aPTT) of 70 seconds (normal range, 28 to 38 seconds), and a prothrombin time (PT) within normal limits.

1. Which one of the following is the next best step to further elucidate the etiology of the patient’s initial clinical presentation?
   a. Thrombin time (TT) testing
   b. Repeat platelet count
   c. Reticulocyte count
   d. Peripheral blood smear
   e. Repeat aPTT

   The patient’s clinical presentation, pertinent hemostatic history, and examination findings are concerning for a clinical bleeding disorder related to abnormalities either in platelet function (primary hemostasis) or in coagulation cascade factors (secondary hemostasis).

   A TT test provides information regarding the final step in the common pathway of the coagulation cascade, in which fibrinogen is converted to fibrin, but as an initial screening test, it does not clarify which portion of the cascade may be responsible for the patient’s unexplained bleeding. In the case of this patient, given that the aPTT is prolonged, we are most concerned for an abnormality in the intrinsic pathway.

   Given that the patient’s platelet count was normal on initial testing, repeating this study would not be helpful.
A reticulocyte count evaluates the number of immature red blood cells in circulation and can be used to calculate a reticulocyte index, which is helpful in narrowing the differential diagnosis of normocytic anemia. However, given that the concern is for a bleeding disorder related to an underlying problem with hemostasis, this would not be of use in this particular clinical context.

A peripheral blood smear is useful in evaluating abnormalities detected on a complete blood count examination. The patient is anemic, which can be explained by the patient’s recent history of bleeding. The next best step in the evaluation of this patient, given the clinical history and laboratory studies available, is to repeat the aPTT measurement to confirm the presence of a derangement in the intrinsic pathway of the coagulation cascade.

Although an abnormality in the coagulation cascade is suggested by the prolonged aPTT, artificial elevations in aPTT are common and can be caused by laboratory variation, several medications including anticoagulants such as heparin, and other congenital and acquired etiologies that influence the clotting cascade such as lupus anticoagulant (LAC). Therefore, a repeat confirmatory test is warranted and would be the next best step.

Both PT and aPTT tests are common laboratory tests ordered in the outpatient setting to assess a patient’s propensity to achieve hemostasis and to evaluate the integrity of the coagulation cascade. A PT test ensures adequate function of the extrinsic and final common pathways of the coagulation cascade, whereas aPTT testing assesses the proper activity of the intrinsic and final common pathways. Traditionally, indications for these laboratory tests include unexplained clinical bleeding episodes (as in this patient), interval monitoring of anticoagulation therapy, assessment of acquired and inherited deficiencies in clotting factor activities, and routine testing of liver function.

After the initial evaluation, further workup included repeat testing, confirming an initially prolonged aPTT of 64 seconds.

2. Which one of the following is the next best test to evaluate the patient’s confirmed prolonged aPTT?
   a. LAC testing
   b. Anti-Xa activity
   c. Mixing study with normal plasma
   d. Reptilase time (RT)
   e. Coagulation factor assays

Antiphospholipid antibodies are a group of antibodies associated with thrombotic events. Within this group, LAC is an antibody that binds to phospholipid-protein complexes and is known to prolong aPTT and other phospholipid-dependent tests. It is typically associated with autoimmune disorders such as systemic lupus erythematosus and connective tissue diseases as well as medications and infections. Clinical manifestations include arterial and venous thromboses, thrombocytopenia in addition to miscarriages, and other symptoms of systemic autoimmune disorders. Diagnosis of LAC involves a screening test for hemostasis, such as aPTT and dilute Russell viper venom time (dRVVT) tests, followed by mixing studies and confirmation of phospholipid dependence. In this case, the patient’s prolonged aPTT should first be evaluated by a mixing study with normal plasma to determine whether the abnormality in hemostasis can be attributed to an inhibitor or coagulation factor deficiency.

Unfractionated heparin is used in many clinical scenarios for both prophylactic and therapeutic anticoagulation. Monitoring of therapeutic unfractionated heparin can be accomplished by aPTT measurement. Alternatively, measurement of anti-Xa activity is another method to monitor continuous intravenous unfractionated heparin therapy. Measurement of anti-Xa activity in this patient would not be helpful, as the patient is currently not treated with anticoagulant therapy and would not
help identify an underlying cause of the patient’s unexplained prolonged aPTT.

Mixing studies, which combine patient plasma with pooled normal plasma, would be the next best step in this situation once a prolonged aPTT is confirmed with repeat studies. Mixing studies would be useful in distinguishing whether a bleeding disorder is due to coagulation factor deficiency or the presence of an inhibitor of one of the coagulation factors. If the aPTT or PT corrects with mixing, then cascade dysfunction is due to factor deficiency, as normal plasma will replace the deficient factor. If the aPTT or PT does not correct, this indicates the presence of a factor-specific inhibitor or a nonspecific inhibitor such as LAC.

A RT test is a test that can be used to further evaluate a prolonged TT and to confirm or exclude the effect of heparin from a patient sample. Other uses of RT include investigation into disorders of fibrinogen. Compared with TT, RT can distinguish between heparin effect (in which case a patient may have a prolonged TT but a normal RT) and true functional fibrinogen disorder (in which case both TT and RT may be prolonged). This patient was not treated with anticoagulant therapy, and RT would not be useful in this setting to confirm or exclude the presence of heparin.

An unexplained prolonged aPTT can be due to coagulation factor deficiency, an inhibitor of coagulation, or attributed to anticoagulant effect. Coagulation factor assays are used to diagnose factor-specific deficiencies, which can be congenital or acquired. The results of coagulation factor assays are typically reported as a percentage of the factor activity level with a normal range. However, in this particular case, an abnormal aPTT should first be evaluated by screening with a mixing study to determine whether prolongation is due to factor deficiency or the presence of an inhibitor. Coagulation factor assays could then be used to investigate whether aPTT prolongation can be attributed to specific factor deficiency.

In our patient, the aPTT did not fully correct to normal range (28 to 38 seconds; decreased from 62 to 41 seconds with mixing), suggesting the presence of an inhibitor in the patient’s serum. Subsequent coagulation factor assays revealed reduced factor VIII activity (5%; normal range, 55% to 200%) and mildly reduced factor XII activity (42%; normal range, 55% to 180%), whereas activities of PTT-dependent factors IX and XI were normal (65% to 140% and 55% to 150%, respectively).

3. Which one of the following best establishes the specific diagnosis in this patient?
   a. Factor VIII inhibitor screen
   b. dRVVT testing
   c. Factor VII chromogenic assay
   d. von Willebrand factor (vWF) antigen
   e. Factor VIII inhibitor screen and Bethesda titer assay

Once the presence of an inhibitor is suspected on the basis of a mixing study that fails to correct, the next best step is to conduct further testing to confirm the presence of an inhibitor. Testing for an inhibitor of factor VIII begins with mixing patient plasma with normal plasma, and factor activity is measured immediately. Decreased activity would be reported as a positive inhibitor screen. Although an inhibitor screen is necessary for antibody identification, quantification with a titer would also be required to determine the strength of inhibition.

The dRVVT test is a test that uses Russell’s viper venom to assess the common pathway of the coagulation cascade by activating factors V and X of the common pathway to bypass the effect of inhibitors or deficiencies of coagulation factors. This test is used to screen for LAC, which is directed toward protein-phospholipid complexes causing similar derangements in aPTT. However, unlike a factor VIII inhibitor, LAC is more likely to cause nonspecific factor inhibition and predispose patients to thrombotic events as opposed to clinical bleeding, which is not the case in this clinical presentation and would not establish a specific diagnosis.

Clot-based assays measure factor activity by using the composite end point of clotting...
time. Testing requires adding patient plasma to factor-specific deficient plasma and measuring the degree of aPTT shortening. The results are compared with a standard curve of dilutions of factor activity and then correlated using a line of best fit. The patient’s above-mentioned factor VIII activity was determined in a similar fashion. An alternative way to measure factor activity is by a chromogenic assay in which a colored substrate is produced after mixing of patient plasma with reagents. Colorimetric absorbance is correlated with a standardized calibration curve to assess factor activity. This method is useful when there is a question of LAC interference to explain aPTT prolongation. However, a chromogenic assay in this case would not establish a specific diagnosis, but is rather an alternative method to determine factor activity, which is already known.

von Willebrand factor is a glycoprotein that is pivotal in primary hemostasis, and von Willebrand disease is a group of inherited bleeding disorders caused by reduced, dysfunctional, or absent vWF. Interestingly, vWF also serves as a carrier for factor VIII and prevents its proteolytic inactivation in the circulation. As a result, decreased vWF levels can also lower factor VIII activity to the point at which aPTT prolongation is observed, causing factor deficiency. The vWF antigen test quantifies the amount of vWF present in plasma, but is not reflective of vWF function. Given that the patient’s aPTT did not correct in a mixing study, factor VIII deficiency is not the cause of a prolonged aPTT and testing vWF antigen for suspicion of von Willebrand disease in this case would not be helpful.

When a factor inhibitor is present on screening, a titer assay is then performed to determine the strength of the inhibitor. These 2 tests in combination would establish a specific diagnosis. A Bethesda titer assay is used to quantify the amount of the inhibitor present in the serum, measured in Bethesda units (BU), where 1 unit is equal to the amount of the inhibitor needed to neutralize 50% of factor VIII in 1:1 mix of serum. In this patient, a factor VIII inhibitor screen was positive, with an inhibitor titer of 22 BU, confirming the diagnosis of a high-titer acquired factor VIII inhibitor.

4. Considering the patient’s diagnosis of a high-titer acquired factor VIII inhibitor, which one of the following is most appropriate for both acute management of the patient’s severe bleeding and long-term immunosuppression?
   a. Activated prothrombin complex concentrate (aPCC)
   b. Factor VIII concentrate
   c. Factor VIII concentrate and prednisone
   d. Desmopressin
   e. Activated prothrombin complex concentrate and prednisone

Once a diagnosis of acquired hemophilia is established, management entails both control of bleeding in the acute setting and long-term immunosuppression, with the ultimate goal of inhibitor eradication. For acute severe bleeding or a high-titer factor VIII inhibitor (>5 BU), aPCC is an option for bleeding control. This product is derived from pooled human plasma and contains factors II, VIIa, IX, and X. Dosing is weight based and varies depending on the type of bleeding and severity. By administering this product, these factors, specifically factor II, in their already activated forms, the inhibition of factor VIII is effectively bypassed, allowing secondary hemostasis to occur. Other options for initial hemostatic management include recombinant human factor VIIa or recombinant porcine factor VIII. However, immediate management would include the use of both a hemostatic agent and an immunosuppressive agent such as glucocorticoids.

For acute treatment of severe bleeding related to a low-titer factor VIII inhibitor (<5 BU), human factor VIII products including factor VIII concentrate and recombinant factor VIII may be used, as there are sufficient levels of factor VIII to overcome the inhibition by the low-level titer. Factor VIII concentrate in combination with prednisone would be an option for a hemostatic agent and immunosuppression, but in this case, the patient has a high-titer factor VIII
level and this regimen would not be the correct choice for management. In the absence of life-threatening bleeding, desmopressin can be used to increase circulating factor VIII levels, although this is rarely recommended.

Eradicating the factor VIII inhibitor requires immunosuppression to stop inhibitor production. This is best accomplished with the use of high-dose glucocorticoids as initial treatment. Additional immunosuppressive agents, such as cyclophosphamide and rituximab (off-label use), can be used in conjunction with glucocorticoids, but are not generally given as single agents. In addition, use of an immunosuppressant alone is not adequate in this situation, as an agent for bleeding control is also needed. Given the above answer choices, the combination of aPCC as a hemostatic agent for initial management of bleeding related to a high-titer factor VIII inhibitor in tandem with a modality for immunosuppression, such as high-dose prednisone, is the best choice for management.

At the initial evaluation, the patient was initiated with 60 mg of prednisone daily but was found to have a 4 g/dL drop in hemoglobin level with imaging evidence of a new left quadratus lumborum hematoma in follow-up, ultimately requiring hospitalization for treatment with 4 doses of aPCC at 50 U/kg for acute bleeding management as well as continuation of prednisone for immunosuppression. Cyclophosphamide was added to his immunosuppression regimen before dismissal.

5. After the initiation of immunosuppression, which one of the following is the most effective approach for frequent monitoring of response to therapy?
   a. Factor VIII levels
   b. Factor VIII inhibitor titer levels
   c. Serial physical examinations
   d. Serial white blood cell counts and absolute neutrophil counts
   e. Serial hemoglobin levels

5. The primary goal of the long-term treatment of acquired hemophilia is elimination of the factor VIII inhibitor. This can be accomplished by monitoring factor VIII activity and aPTT levels. Generally, these tests correlate, but given that the sensitivity of the aPTT to factor VIII deficiency varies with reagents, factor VIII levels are recommended to monitor response to therapy.

Factor VIII inhibitor titers often decrease relatively slowly and are expensive and time-consuming to perform serially in the laboratory. Although monitoring factor VIII inhibitor titer at the completion of treatment to ensure inhibitor eradication is recommended, frequent monitoring of aPTT and factor VIII activity levels is more helpful and cost-effective.

Serial physical examinations for monitoring evidence of bleeding are helpful in the management of acute treatment of acquired hemophilia when severe bleeding is suspected or has occurred, but do not help in monitoring of long-term response to inhibitor suppression therapy. Frequent monitoring of the white blood cell count with differential to quantify absolute neutrophil counts and hemoglobin levels while receiving immunosuppression or monitoring of clinical bleeding is not necessary. During follow-up after hospitalization, the patient’s aPTT was 42 seconds (28 to 38 seconds) and the factor VIII activity level was 41% (55% to 200%) with interval clinical improvement at which time he was continued on prednisone and cyclophosphamide for immunosuppression. He continued to be closely followed by hematology every month and, after stabilization, every 3 months to monitor for relapse.

DISCUSSION

Acquired factor VIII inhibitor, also known as acquired hemophilia A (AHA), is a rare autoimmune condition with an incidence of approximately 1.3 to 1.5 in 1 million. It is most commonly seen in adults older than 50 years.

Acquired hemophilia A occurs when autoantibodies (typically IgG) form, which bind to factor VIII and prevent binding to a phospholipid. The exact etiology of these autoantibodies is unclear, but many
conditions have been described as risk factors including pregnancy, autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus, malignancy, and certain medications such as penicillin, phenytoin, fludarabine, and interferon. However, 50% of cases remain idiopathic. Clinically, signs and symptoms involve non-traumatic bleeding, including extensive ecchymosis, hematomas, and epistaxis. Additional clinical features may include occult gastrointestinal bleeding, gross hematuria, and/or bleeding out of proportion to that expected for a given surgical procedure. Unlike congenital hemophilia A, hemarthrosis is quite uncommon with AHA.

In AHA, an isolated elevation of aPTT indicates dysfunction of the intrinsic pathway of the coagulation cascade. The differential diagnosis for this laboratory pattern of coagulation studies includes an artificial elevation in aPTT, factor deficiency, coagulation factor inhibitor, LAC, von Willebrand disease, or the use of anticoagulants, specifically heparin products. Mixing studies for the assessment of appropriate aPTT correction provides further insight into whether the cause of bleeding is related to coagulation factor deficiency or the presence of an inhibitor. Specific coagulation factor deficiencies can be further elucidated with coagulation factor assays to determine factor activity. Inhibitor screening can further clarify the difference between drug effect, nonspecific inhibitors, and factor-specific inhibitors. For AHA, the Bethesda titer assay is used to quantify the inhibitor titer with the number of serial dilutions of both patient plasma and normal plasma that are needed to achieve 50% of factor VIII activity in Bethesda units.

Management of acute bleeding depends on the severity as well as the inhibitor titer level. Low-titer inhibitor bleeding (<5 BU) can be managed with replacement of factor VIII, with monitoring of factor VIII activity thereafter. High-titer inhibitors require treatment with a bypassing agent such as aPCC or recombinant factor VIIa for management; although there are no prospective trials comparing these 2 therapies, registry trials suggest that both achieve similar bleeding control.

In conjunction with acute bleeding control using the above strategies, inhibitor suppression is an important pillar of long-term management. Given the rare incidence of this condition, there are no large randomized clinical trials guiding the use of particular agents but steroids are commonly used alone or in combination with cyclophosphamide or rituximab (off-label). Clinical response is defined as an undetectable inhibitor level, a factor VIII level greater than 70 IU/mL, and the ability to discontinue immunosuppression. Based on registry data, clinical response to first-line immunosuppression was observed at a median of 32 to 34 days with steroids alone and at 32 to 40 days when steroids were combined with cyclophosphamide. Complete remission, defined by the discontinuation of immunosuppression, was achieved at a median of 108 days for patients treated with steroids alone (45%) as compared with 74 days for those treated with both steroids and cyclophosphamide (80%). Relapse rates were higher for those treated with steroids (18%) than for those treated with both steroids and cyclophosphamide (12%).

In the appropriate clinical context, an elderly patient with significant unexplained bleeding and no history of bleeding events should raise a clinician’s suspicion for an underlying acquired autoantibody. The diagnosis of acquired factor VIII deficiency can certainly be elusive, particularly because of the rarity of the disorder. Despite this, it should remain part of the differential diagnosis in patients presenting with spontaneous bleeding, especially in older patients who have an unexplained isolated prolonged aPTT without other laboratory abnormalities.

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REFERENCES


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