Case Report

Acquired Haemophilia due to Factor-VIII Inhibitors Secondary to Bladder Malignancy: A Case Report

***Shabana Shumail, *Dr. Ayesha Junaid, **Dr. Kamran Rashid**
*Hematology Department, **Oncology Department Shifa International Hospital Islamabad, Pakistan

Abstract: Acquired hemophilia A (AHA) is a severe bleeding diathesis caused by the appearance of autoantibodies against coagulation factor VIII (FVIII). Clinical features of inherited and acquired hemophilia are spontaneous as well as posttraumatic deep muscle-joint and mucosal bleeding. 50% cases of AHA are associated with autoimmune diseases, malignancies, medications and the postpartum period, but in the rest of the patients development of FVIII autoantibodies is idiopathic. Unexplained prolonged activated partial thromboplastin time (APTT) without previous history of bleeding should warrant work up for AHA. AHA secondary to bladder malignancy is rare with only three cases reported till to-date. We report a case of an elderly male who developed acquired hemophilia secondary to bladder malignancy and presented with a rare clinical presentation of hemarthrosis.

Key Words: Acquired hemophilia A (AHA), Factor VIII, Partial Thromboplastin Time

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Introduction

Acquired factor VIII inhibitor is a rare occurrence and serious cause of life and limb threatening hemorrhages. Factor VIII is an X-linked gene product which in the presence of calcium and phospholipids combines with factor IXa, and then activates factor X. For coagulation cascade factor VIII acts as a catalyst. Absent or reduced levels of factor VIII can be an inherited condition referred to as classic hemophilia A. The likely clinical features of inherited and acquired hemophilia are easy bruising and deep muscle-joint and posttraumatic bleeding. Milder cases are not evident until there is a traumatic or surgical challenge in the second or third decade of life. A severe case is usually diagnosed after circumcision or unexplained intracranial hemorrhage within the first year of life.[1]In non-hemophilic population the incidence of acquired inhibitors against FVIII is 1 to 4 per million/year.

Author's Correspondence
Shabana Shumail
shaby2012@gmail.com
Department of Hematology
Shifa International Hospital Islamabad

Severe or life-threatening bleeding occurs in upto 90% of patients and typically occurs early in the course of the disease with mortality rates between 8 and 22%.[2] Acquired hemophilia is generally diagnosed after detection of an isolated prolonged activated partial thromboplastin time (APTT), which fails to correct on mixing studies, and subsequent finding of decreased FVIII levels and presence of FVIII inhibitor. In up to 50% of the patients the inhibitors are associated with autoimmune diseases, malignancies, medications, or the postpartum period, but in most patients development of FVIII autoantibodies is idiopathic. [3-4] Age distribution is bimodal, with a first peak occurring among young adults, due to cases in women in the postpartum period. Second major peak occurs in elderly patients, frequently associated with malignancy and drugs which is very difficult to manage due to the comorbidities and the "fragility" of the older individuals.[5] The treatment of the underlying diseases often corrects the coagulation disturbances by eradicating the inhibitors. The bleeding pattern in acquired hemophilia is different from that of congenital hemophilia A with increased bleeding tendency in soft tissue, muscle, retroperitoneal space, and gastrointestinal or genitourinary tracts. Hemarthrosis is a rare occurrence in acquired

hemophilia A. Thus a prompt recognition with early and aggressive treatment of this disorder is crucial, as diagnostic delays or inadequate treatments are associated with high mortality rates.[6] The principles of treatment are to control bleeding, primarily with recombinant factor VIIa (rFVIIa). Long-term eradication of autoantibodies is achieved by immunosuppression using a combination of steroids, cyclophosphamide, intravenous immunoglobulins and monoclonal antibodies.[7, 8] Here we report a case of an elderly male with acquired hemophilia secondary to malignancy who developed a rare presentation of hemarthrosis.

Case Presentations

An 86-year-old male with a history of diabetes, hypertension, gout, Ischemic heart disease, and on chronic allopurinol treatment for gout presented to urology department of our hospital with the complaint of hematuria. His work up for hematuria revealed bladder mass. He was planned for Transurethral Resection of Bladder Tumor (TURBT) but could not be performed due to isolated increased activated part al thrombin time (aPTT) of 70s (normal 26.1–33.5 s) and a normal prothrombin time (PT) of 11.30 s (10.0–12.4 s). During the course of his workup he developed swelling of left knee extending to the left calf and leg along with diffuse bruising, which made the patient bed bound. Laboratory investigations revealed a hemoglobin of 5.9 g/dl, total leucocyte count of 20 $x10^9$ /l, normal platelet count and INR was also within normal limits. Workup for anemia showed normal iron profile, vitamin B12 and Folate levels. Negative coomb's test and normal reticulocyte count ruled out the possibility of hemolytic anemia. Provisional diagnosis of Anemia of unknown cause, Sepsis, Acute Kidney Injury and septic arthritis were made for which orthopedic consult was done. Left knee arthrocentesis was done which showed frank blood and culture of synovial fluid did not show any growth. Patient was transfused with multiple packed red cells but hemoglobin kept falling after temporary improvement. A diagnosis of left knee hemarthrosis was made and haematology consult was done. Due to isolated prolonged APTT mixing study was ordered. Mixing study confirmed the presence of inhibitors. To determine the underlying etiology autoimmune profile, lupus anticoagulant and viral screening were carried out which were negative. A renal ultrasound scan was also normal. It was postulated that the most likely explanation for the acquired hemophilia was his bladder cancer. So a final diagnosis of Acquired hemophilia with development of factor VIII inhibitors secondary to bladder malignancy was made. Patient was initially managed with intravenous steroid (Inj. Methyl prednisolone 100mg I/V one daily) for 10 days. However the patient developed two episodes of spontaneous hematomas in left cubital fossa and elbow due to which his hemoglobin dropped from 9 g/dl to 7 g/dl. Acute bleeding episode was managed with recombinant factor VII (Inj. Novo seven at a dose of 90mcg/kg) through intravenous bolus injection. As there was no response to 1st line therapy, second line therapy with monoclonal anti CD20 antibody was started, to which the patient responded very well. His knee swelling improved without any new bleeding episode. His hemoglobin improved and remained stable at 10 g/dl. After two courses of therapy his APTT dropped down to 27 sec. His WBC count and CRP also improved. With intensive physiotherapy patient was mobilized and discharged with an advice to follow up for subsequent chemotherapy cycles and further management of bladder mass. He was maintained on prednisolone. His follow up APTT test results were normal with undetectable FVIII inhibitors. During follow up his TURBT was done and cold cup biopsy was taken, which was reported as Papillary Urothelial Carcinoma (Fig 1 & 2).

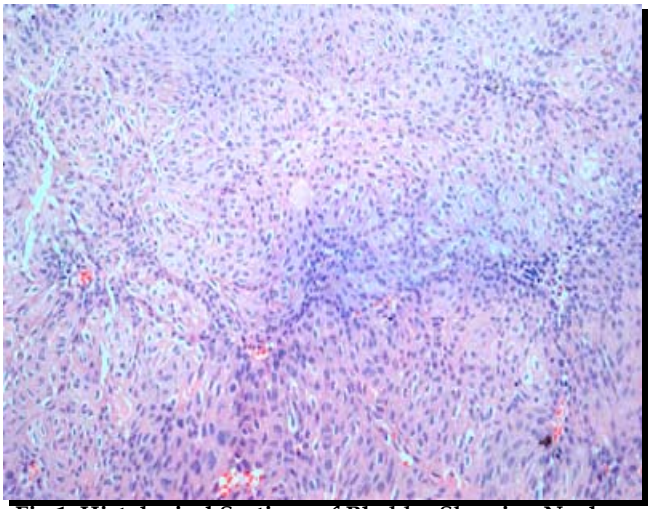

Fig.1: Histological Sections of Bladder Showing Nuclear Pleomorphism (Magnification 20x)

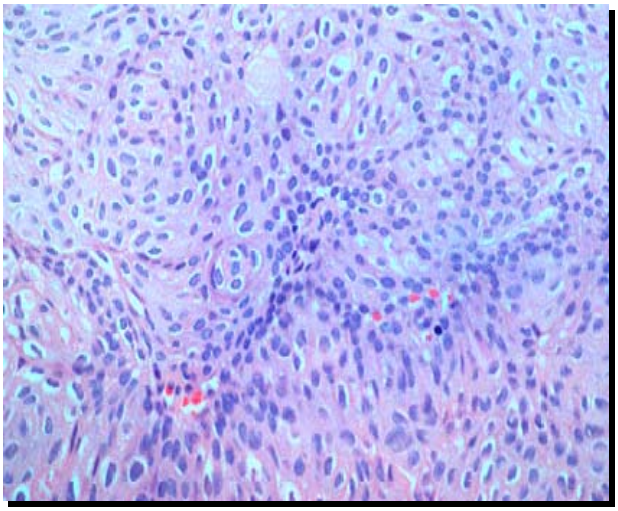

Fig.2: Histological Sections of Bladder Showing Nuclear Pleomorphism (Magnification 40x)

Discussion

We described a case of Acquired Hemophilia with different clinical features, underlying pathology, and response to treatment. The bleeding phenotype in this patients ranged from isolated prolonged APTT with no bleeding tendency to severe hemarthrosis necessitating rVIIa infusion and blood components transfusion. The occurrence of hemarthrosis in this case is unusual, however there are other reports of a similar presentation [9].

Acquired Factor VIII inhibitors is an auto-immune occurrence where autoantibodies against a domain on the factor VIII protein are produced. These autoantibodies block or reduce the avidity of the protein to bind to its cofactors, factor X, factor IXa and von Willebrand factor[1]. The etiology is variable, and up to half of cases are still considered to be idiopathic in nature. The conditions associated with the production of factor VIII autoantibodies include pregnancy, other autoimmune diseases such as systemic lupus erythematosus, inflammatory bowel disease, diabetes, acute hepatitis B & C and varied malignant conditions. The presentation of Acquired factor VIII deficiency/inhibitor is discordant to the presentation of hemophilia A. Early age of onset and spontaneous hemarthrosis are pathognomonic of congenital hemophilia, but are quite rare in acquired disease. The natural history of acquired factor VIII inhibitors is varied. When associated with pregnancy the presentation is within two to three months postpartum with most cases associated with the first pregnancy i.e. in primigravidas. Acquired hemophilia is associated with underlying malignancies in 7-15 percent of cases with increased prevalence associated with solid tumors than hematological malignancies. However no specific solid tumor has been attributed to development of antibodies. [3, 7, 8, 10]

Reitter et al analysed cases of cancer-associated FVIII autoantibodies and documented that these autoantibodies develop following cancer surgery. However they also revealed the cases where acquired hemophilia was diagnosed prior to surgery. Literature shows that 32% of cases were associated with urological malignancies with prostate cancer the most prevalent amongst all cancer types. AHA due to underlying bladder cancer is extremely rare. Only three cases have been reported till date that developed FVIII autoantibodies following bladder tumor. [11,12] Kreuter et al reported development of autoantibodies in a patient following resection of a rectal tumor in the first case. This patient underwent resection of a bladder tumor 6 months later. [13] Second patient had concomitant bladder and renal tumors. [14] Fitzpatrick J reported a case of acquired hemophilia secondary to transitional cell carcinoma of the bladder. [12]

Due to rarity and clinical diversity of this disease entity, the treatment of acquired hemophilia is tricky. Management plans are tailored on a case-by-case basis. However, generally accepted principles of management are to control the acute bleeding events, avoid invasive procedures that may provoke extra bleeding, eliminate FVIII inhibitor through immunosuppression and treat the underlying disease. To control the acute bleeding, two main first-line agents that are licensed for the treatment are rFVIIa (NovoSeven) and activated prothrombin complex concentrate (aPCC). [15] To eradicate the inhibitor the strategy of corticosteroids alone or corticosteroids in combination with cyclophosphamide is used. If disease is not in remission with corticosteroids or cyclophosphamide then third-line immunosuppressive agents such as Rituximab can be introduced, as was the case in our patient. Although immunosuppressive therapy is eminent in inducing remission of AHA but to treat the underlying disease is of cardinal importance.

Conclusion

For the differential diagnosis of acquired hemophilia, bladder tumors should be a consideration if all other causes have been excluded, as bladder tumors tend to bleed a lot and there may be occurrence of post-resection bleeding as well.

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