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Case Report
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Acquired von Willebrand Disease in Multiple Myeloma - A Case Report and Review of Literature

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Abstract

Acquired von Willebrand Disease (avWD) is an exceedingly rare bleeding disorder in contrast to congenital von Willebrand Disease (vWD) with an estimated prevalence of 0.04% to 0.13% in the general population. It is commonly associated with underlying lymphoproliferative or myeloproliferative disorders like Monoclonal Gammopathy of Undetermined Significance (MGUS), Waldenström macroglobulinemia and multiple myeloma. We report a patient with multiple myeloma who developed severe avWD while undergoing autologous Peripheral Blood Stem Cell Transplant (PBST). A forty-nine-year-old gentleman with history of hypertension and no significant personal or family history of bleeding disorder was diagnosed with multiple myeloma (IgG kappa) ISS III. He attained Complete Response (CR) after 6 cycles of Bortezomib, Lenalidomide and Dexona (RVD) regimen and was scheduled for consolidation with High Dose Chemotherapy (HDCT) and autologous Peripheral Blood Stem Cell Transplant (PBST). Just before administration of stem cells, he developed bleeding from the subclavian catheter site. Evaluation of coagulopathy showed prolonged activated Partial Thromboplastin Time (aPTT), normal Prothrombin Time (PT), reduced vWF (16%) and factor VIII (20%) activity and normal factor IX and XI, suggestive of severe avWD. He was continued on maintenance chemotherapy and later underwent HDCT and PBST with blood product support (cryoprecipitate, fresh frozen plasma and apheresis platelets). He was also given intravenous immunoglobulin before catheter insertion. The procedure was uneventful. This subject had severe AvWD despite adequate treatment for multiple myeloma and showed good response to immunoglobulin. He underwent autologous PBST and never reported any further bleeding episode and is currently on follow up. Prompt identification and treatment of the underlying disorder is necessary apart from clinical management of avWD.

Keywords: Acquired von Willebrand disease; Multiple myeloma; von Willebrand factor; Monoclonal gammopathy; Autologous peripheral blood stem cell transplant

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Introduction

von Willebrand Factor (vWF) is a circulating high molecular weight glycoprotein, synthesized by the endothelial cells and megakaryocytes which plays an important role in hemostasis through interaction with Glycoprotein (GP) Ib-IX receptor complex in platelets [1]. It is also secreted into the circulation where it acts as a carrier protein for procoagulant factor VIII in blood thereby stabilizing it and forms a complex which plays a role in fibrin clot formation [1,2]. Quantitative or qualitative abnormalities of vWF can result in von Willebrand Disease (vWD), the most common inherited bleeding disorder [3]. Acquired von Willebrand Disease (avWD) is an exceedingly rare bleeding disorder in contrast to congenital von Willebrand Disease (vWD) with an estimated prevalence ranging from 0.04% to 0.13% in the general population [4].

It is commonly associated with underlying lymphoproliferative or myeloproliferative disorders like Monoclonal Gammopathy of Undetermined Significance (MGUS), Waldenström macroglobulinemia or multiple myeloma [4,5]. In multiple myeloma, the paraprotein produced by the clonal plasma cells is believed to be involved in the pathogenesis of avWD [4]. We report a patient with multiple myeloma who developed severe avWD while undergoing High Dose Chemotherapy (HDCT) and autologous Peripheral Blood Stem Cell Transplant (PBST).

Case Presentation

A 49-year-old gentleman with history of hypertension and no significant personal or family history of bleeding disorder was diagnosed with multiple myeloma (IgG kappa) ISS III. Once he attained Complete Response (CR) after 6 cycles of Bortezomib, Lenalidomide and Dexona (RVD)

regimen, he was scheduled for consolidation with HDCT and autologous PBST. Hematology and clotting profiles were normal and stem cells were mobilized with Granulocyte Colony Stimulating Factor (GCSF). Just before administration of stem cells, he developed bleeding from the subclavian catheter site. His platelet count dropped to a nadir of 69000, probably GCSF/apheresis induced.

He was evaluated for coagulopathy which showed prolonged activated Partial Thromboplastin Time (aPTT) with normal Prothrombin Time (PT). His Clotting Time (CT) was 10 min. In view of persistent bleeding and suspected coagulopathy, procedure was deferred after informed consent. Catheters were removed under transfusion support. Further work up for coagulopathy showed reduced vWF (16%) and factor VIII (20%) activity with normal factor IX and XI suggestive of severe avWD. He was continued on maintenance chemotherapy with bortezomib and hematology opinion was sought. He later underwent HDCT and PBST with blood product support (cryoprecipitate, fresh frozen plasma and apheresis platelets) and received intravenous immunoglobulin before catheter invasion. The procedure was uneventful and he did not develop any further bleeding manifestation. He completed 2 years of maintenance and is currently on follow up.

Discussion

von Willebrand disease is the most common inherited bleeding disorder transmitted as an autosomal dominant trait [3]. It is caused by mutation in the vWF gene which leads to quantitative or structural abnormalities of vWF [6]. Acquired von Willebrand disease occurs in adults with no previous personal or family history of bleeding disorder seen commonly in association with lymphoproliferative or myeloproliferative disorders [4,7,8]. Registry data from International Society of Thrombosis and Hemostasis (ISTH) notes lymphoproliferative disorders as the most common underlying cause (48%) of avWD [9]. The association between monoclonal gammopathy and avWD was first described by Ingram et al. [10]. Mohri et al. [11] notes that three out of 42 patients with multiple myeloma had avWD. It is more commonly seen in men than women of advanced age [12]. Our patient was a middle-aged gentleman.

The pathogenesis of avWD in multiple myeloma is not clearly studied. In multiple myeloma, autoantibodies against functional domains of vWF is the most likely cause of avWD. Other probable mechanisms include formation of immune complexes between antibodies and vWF resulting in accelerated catabolism or elimination and selective adsorption of vWF by tumor cells on their surface leading to depletion of vWF in circulation [13-15]. The presence of autoantibodies is demonstrated through inhibition of ristocetin cofactor activity of normal plasma [4]. The inhibitory antibodies commonly recognize the factor VIII:vWF complex though antibodies that bind to vWF alone also has been reported resulting in normal factor VIII activity but no measurable vWF activity [16]. IgG kappa is the most common immunoglobulin fraction associated with avWD followed by IgM and rarely IgA [17-19]. Our patient had IgG kappa disease and inhibitory antibodies against factor VIII:vWF complex being the most likely pathogenesis in view of reduced vWF and factor VIII activity which resulted in avWD.

In the absence of significant personal or family history of bleeding disorder, the presence of an underlying dysproteinemia, a lymphoproliferative or a myeloproliferative disorder as reported in this subject gives a diagnostic clue to the presence of avWD. Specific laboratory tests include plasma vWF antigen and ristocetin cofactor activity. Bleeding time, clotting time, screening tests for coagulation (aPTT, PT) and factor VIII activity lack sensitivity and specificity [4]. Our patient had multiple myeloma and was planned for HDCT and PBST when he developed bleeding from catheter insertion site. He had prolonged aPTT and CT with reduced vWF and factor VIII activity suggestive of avWD.

The crux of clinical management in avWD aims at preventing bleeding in patients having invasive procedures, symptomatic treatment of those who had bleeding and treatment of underlying disorder. Desmopressin, concentrates containing vWF and factor VIII are used for the treatment of bleeding. The treatment of multiple myeloma may permanently reverse the bleeding disorder as reported by Mohri et al. [11] although the responses are unpredictable [20]. High dose immunoglobulin has been shown to produce rapid and sustained responses in those patients not responding to desmopressin or treatment of underlying disease [11]. The exact mechanism is unknown, probably related to an effect on the clearance of vWF-antibody complex in avWD [21]. This subject had severe avWD despite adequate treatment for multiple myeloma and showed good response to immunoglobulin. He later underwent autologous PBST which was uneventful and never reported any further bleeding episodes.

Conclusion

Acquired von Willebrand disease is a rare bleeding disorder commonly associated with underlying lymphoproliferative disorders. Prompt identification and treatment of the underlying disorder is necessary apart from clinical management of avWD. Intravenous immunoglobulin is useful in those not responding to treatment or in those who are undergoing invasive procedures.

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