Acquired von Willebrand's Syndrome in a Patient with Concomitant Chronic Lymphocytic Lymphoma and Smoldering Multiple Myeloma

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ABSTRACT

An African-American female in her sixties presented to the hospital with intermittent gum bleeding for the past two years along with severe anemia. This case details the differential and workup that lead to the diagnosis of acquired von Willebrand's syndrome (AvWS). A thorough investigation in the possible etiologies of AvWS revealed that the patient had concomitant chronic lymphocytic lymphoma (CLL) and smoldering multiple myeloma (SMM). Due to the concomitant diagnosis of CLL and SMM, there was a dilemma regarding whether CLL, SMM, or both was driving this patient's AvWS. Decision was made to treat the underlying CLL initially with rituximab and later on at recurrence with obinutuzumab/venetoclax with complete resolution of patient's bleeding and normalization of her factor VIII activity, von Willebrand factor antigen levels, and vWF:ristocetin cofactor levels. We believe this is first case in the literature of a patient with AvWS with concurrent CLL and SMM.

KEYWORDS: Acquired von Willebrand's Syndrome, chronic lymphocytic lymphoma, smoldering multiple myeloma

BACKGROUND

The case details the differential and workup that led to the diagnosis of acquired von Willebrand's syndrome (AvWS) in a patient presenting with mucocutaneous bleeding without any previous personal or family history of bleeding. Through this case, the authors have attempted to go over the etiologies of AvWS, and systematically explain how the diagnosis of chronic lymphocytic lymphoma (CLL) and smoldering multiple myeloma (SMM) were made while ruling out other differentials. Due to the concomitant diagnosis of CLL and SMM, there was a dilemma regarding whether CLL, SMM, or both was driving this patient's AvWS. In the case, the authors discuss how this dilemma was addressed, how treatment modalities were selected, and how the patient was monitored. At the end, the authors compare AvWS in this case with previously reported cases of AvWS in patients with CLL. We believe this case presents a unique diagnostic challenge and dilemma, and we have attempted to provide a step-by-step clinical reasoning to address the multiple facets of the case.

CASE PRESENTATION

An African-American female in her sixties with a past medical history of hypertension and hypothyroidism presented to the hospital with symptoms of fatigue, dyspnea on exertion, and bleeding from the gums. She reported intermittent gum bleeding for the past two years and became concerned the day prior to admission when the bleeding did not stop. She was hemodynamically stable, with an exam significant for pale conjunctiva and no lymphadenopathy or hepatosplenomegaly. Of note, the patient denied any personal or family history of bleeding, transfusion, menorrhagia, or hemarthrosis.

INVESTIGATIONS

Initial laboratory workup showed hemoglobin of 3.5g/dL, hematocrit 11.7%, MCV 90fL, WBC 15.8 x 10e9/L, platelets 326 x 10e9/L, and reticulocyte index 1.65. Iron panel was consistent with iron deficiency anemia with an iron < 10 ug/dL, iron saturation was low at a level that could not be quantified, TIBC 434 ug/dL, and ferritin 8 ng/ml. Additional lab work revealed normal PT, PTT, thrombin-time, and fibrinogen. CT face and CTA abdomen, pelvis with and without contrast were unremarkable for any bleed or acute pathology.

The presence of mucocutaneous bleeding in the setting of a normal platelet count and coagulation profile led to further workup of an acquired bleeding diathesis. This evaluation revealed factor VIII activity of 59% (reference range 50–150%), von Willebrand factor antigen 35% (reference range 50–180%), vWF:ristocetin cofactor 10% (reference range 40–180%), vWF:collagen binding 10% (reference range 50–200%), PFA-collagen/epinephrine > 232 seconds (reference range 75–195 seconds), and PFA-collagen/ADP > 300 seconds (reference range 70–120 seconds). A vWF propeptide antigen was also performed and found to be 86 IU/dL (reference range 62–183 IU/dL).

DIFFERENTIAL DIAGNOSIS

The differential for acquired bleeding disorders can be broadly divided into platelet disorders and coagulation cascade disorders.[1,2,3] Platelet disorders can be further divided into quantitative or qualitative defects. This patient's platelet levels were within normal levels making quantitative platelet disorder less likely. The normal comprehensive metabolic panel made renal and liver diseases unlikely etiologies of her presentation. At this point, platelet dysfunction and acquired coagulation cascade disorders were differential diagnoses. The normal PT/INR and PTT argued against an acquired factor deficiency. Additionally, the patient's ISTH bleeding assessment tool score of 4 made an inherited bleeding disorder less likely.

Although the patient's pro-peptide to VWF ratio was less than 3.9, it was felt that she still likely had AvWS because of her late onset mucocutaneous bleeding history and lack of family bleeding history. In order to elucidate the etiology of AvWS she underwent evaluation for hypothyroidism, lymphoproliferative disorders, myeloproliferative disorders, and structural cardiac diseases for etiologies commonly associated with AvWS.[4,5,6]

Transthoracic echocardiography was performed and was unremarkable. She had TSH of 10.2 uIU/ml with decreased total T3 62 ng/dl (80–180 ng/dl) and normal T4 1.15 ng/dL (0.8–1.8ng/dL). SPEP detected a monoclonal paraprotein in the gamma region (0.67g/dL). She was found to have normal serum kappa light chain levels, elevated lambda light chain levels, and decreased kappa/lambda ratio (0.16). Immunofixation revealed monoclonal IgG-lambda.

Flow cytometry and immunophenotypic analysis of peripheral blood and bone marrow were done. Analysis of peripheral blood showed 60% CD19+ B-lymphoid cells co-expressing CD5 and exhibiting cytoplasmic Ig kappa light chain restriction (absolute number 1.5 x 10e9/L). They were positive for CD20 (dim), CD22, CD23, CD11c, CD25, CD38, CD52, and CD79b (dim) and negative for CD10, CD103, and FMC7. Bone marrow aspirate analysis showed hypercellular bone marrow with trilineage hematopoiesis. Immunohistochemistry showed approximately 40% PAX5+, kappa+, minimally CD20+ B- lymphoid cells, approximately 10-15% CD3+, CD5+ T-cells, and approximately 15-17% CD138+ plasma cells. The plasma cell population was in a large subset lambda light chain restricted and co-expressed cyclin D1. Flow cytometry of bone marrow aspirate identified 15% lymphocytes of all bone marrow white blood cells and a large subset (77%) being cytoplasmic Ig kappa light chain restricted B-lymphoid cells co-expressing CD5 and CD19, dim CD20 positive.

Based on analysis of the peripheral blood and bone marrow, the patient was diagnosed with chronic lymphocytic lymphoma (CLL) based on International Workshop in Chronic Lymphocytic Leukemia (iwCLL) guidelines, as it was thought her B cell clonal process was driving her symptoms. Cytogenetics were significant for trisomy 12 and IgHV was unmutated. Additionally, her bone marrow contained 15–17% mostly lambda chain restricted plasma cells consistent with a diagnosis of smoldering multiple myeloma (SMM) given the absence of hypercalcemia, renal dysfunction, and bone lesions. Her severe microcytic anemia on presentation was secondary to iron deficiency.

TREATMENT

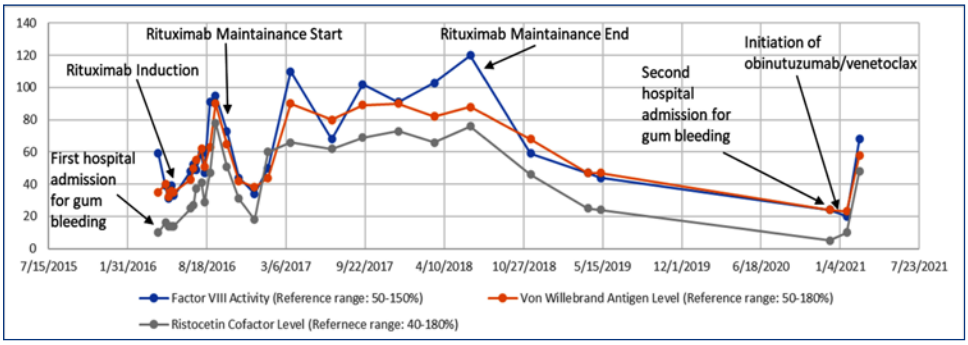
Treatment of her AvWS was two pronged to first stop the bleeding, and secondarily to treat the underlying cause. Tranexamic acid 1300mg PO three times daily sufficiently stopped bleeding. At diagnosis, however, it was unclear whether CLL, SMM, hypothyroidism or all three were driving this patient's AvWS. It was thought that the patient's hypothyroidism was less of a factor in this situation because the patient's VWF profile was more in keeping with an inherited type 2 VWD panel (much lower activity level to antigen level), which is what is often seen in lymphoproliferative disorders and multiple myeloma. AvWS with hypothyroid usually fits an inherited type 1 VWF panel profile (lower antigen to activity level). She was started on thyroid supplementation with levothyroxine, which corrected her hypothyroidism but it did not normalize her factor VIII activity (FVIII activity), von Willebrand factor antigen levels (vWF:Ag), and vWF:ristocetin cofactor (vWF:RCo) levels. Hence, it was determined that hypothyroidism may have been contributing but was not the major driver of the patient's AvWS.

The patient was initially risk stratified for both CLL and SMM based on the most recent evidence-based guidelines available at the time with the thought that an underlying reason to treat one or the other would help guide therapy.[7,8,9] Although she presented with anemia, which would have made her a high risk on both Rai and Binet staging systems for CLL,[10,11] with initial pRBC transfusion and subsequent control of gum bleeding with tranexamic acid, her hemoglobin returned to normal consistent with her anemia being secondary to iron deficiency. Given that she also had no lymphadenopathy, she was thus classified as low risk CLL. Additionally based on the Mayo Clinic SMM risk stratification she was low risk for myeloma as well.[8,9]

Left with no clear evidence for symptomatic CLL or SMM we reviewed her presenting lab values which showed a normal vWF propeptide antigen. This suggests that this patient's low vWF levels were secondary to increased clearance, which we postulated was an antibody-mediated phenomenon.[12] We therefore targeted this potential lymphoid B-cell antibody production with rituximab.

She received weekly rituximab for four weeks. FVIII activity, vWF:Ag, and vWF:RCo levels showed improvement compared to the patient's baseline at initial hospital presentation. She was then treated with rituximab maintenance

Figure 1. Factor VIII activity, Von Willebrand antigen level, and ristocetin cofactor level in response to rituximab and subsequently to obinutuzumab/venetoclax.



every three months for two years with normalization of her FVIII activity, vWF:Ag, and vWF:RCo levels during the maintenance (**Figure 1**). She did not report any bleeding during this time period.

OUTCOME AND FOLLOW-UP

She was subsequently lost to follow-up after discontinuation of rituximab. Almost two years after discontinuation of rituximab, the patient presented to the outpatient clinic for bleeding from the gums. Flow cytometry was performed and found consistent with prior flow cytometry results. SPEP, kappa/lambda ratio, and immunofixation continued to show stable monoclonal IgG lambda.

Considering that while being on maintenance rituximab the patient's AvWS resolved while SMM remained untreated in the background, it was determined that the recurrence of AvWS was again secondary to CLL rather than SMM. She was started on CLL-directed therapy once again with obinutuzumab and venetoclax. After starting the obinutuzumab/venetoclax regimen, the patient's levels of FVIII activity, vWF:Ag, and vWF:RCo once again returned to normal levels and her bleeding subsided.

DISCUSSION

To our knowledge, this is the first case in the literature of a patient with AvWS who was concurrently diagnosed with CLL and SMM. It highlights clinical dilemmas in elucidating the etiology of AvWS, the decision to observe or treat CLL and SMM, and which treatment modality to pursue when presented with confounding etiologies.

AvWS is not an indication for treatment based on latest guidelines by International Workshop on Chronic Lymphocytic Leukemia (iwCLL).[13] It is also not an indication for treatment based on Mayo Clinic criteria for SMM.[14] Our patient did not fulfill any criteria for "active disease" as defined by iwCLL. Additionally per Mayo 2018 risk-stratification system (also called the 20/2/20 criteria), our patient was low risk for SMM and thus observation was recommended. In situations similar to our patient's where underlying lymphoproliferative disorder is low risk, we believe an individualized approach should be pursued weighing the benefit of treating AvWS versus risk from the chemoimmunotherapy. Patients with mild occasional mucocutaneous bleeding can be managed symptomatically with desmopressin (DDAVP), vWF/FVIII concentrates, or antifibrinolytics such as aminocaproic acid or tranexamic acid. However, patients with significant bleeding or those who may require multiple surgeries/procedures in the future may benefit from treating underlying CLL, SMM, or both. Our patient had significant bleeding which resulted in profound anemia with hemoglobin of 3.5g/dL necessitating therapeutic intervention.

When presented with multiple possible etiologies for AvWS, it becomes important to decipher the underlying cause and then decide on appropriate treatment. In our case, initially it was unclear whether hypothyroidism, CLL, SMM, or a combination of the three was driving the AvWS. Considering that the patient's hypothyroidism resolved with levothyroxine without any change to her levels of FVIII activity, vWF:Ag, and vWF:RCo, it was felt that hypothyroidism was not the driving etiology of her AvWS. Although a significant number of patients diagnosed with AvWS have lymphoproliferative disorder, the exact prevalence remains unclear. Estimates range from 18–48%. Same studies have shown prevalence of MGUS in 14–23% of patients, and multiple myeloma in 2–9% of patients.[6]

We felt that the best way to determine the etiology of AvWS in our patient would be to target CLL first considering prior case reports linking CLL to AvWS. Thus far we have not come across any prior case report with association between SMM and AvWS. Alattar et al reported three cases of AvWS in patients with CLL.[15] Compared to our case, all three patients were diagnosed with CLL prior to eventual workup and identification of AvWS. Additionally compared to our patient who did not have "active disease" per iwCLL criteria, all three cases had "active disease" when treatment was initiated. The patient in case one was diagnosed with AvWS three years after development of CLL. Her AvWS symptoms were managed with aminocaproic acid mouth rinses until about two years later her CLL progressed, and she was treated with lenalidomide and rituximab. In case two, the patient with a history of severe melena secondary to duodenal bleeding was diagnosed with CLL after developing bulky lymphadenopathy. He was initially treated with a combination of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone. About four years later after a

second round of salvage therapy, the patient presented with GI bleed, and the workup revealed AvWS. In case three, the patient with CLL treated with fludarabine, cyclophosphamide, and rituximab was found to have prolonged bleeding after surgery and excision of his metastatic melanoma. He was ultimately diagnosed with AvWS. Khalife et al report a case of a patient who experienced multiple recurrent epistaxis about two years after the diagnosis of his CLL.[16] Patient was treated with chlorambucil and obinutuzumab with remission in both CLL and AvWS.

In a case of AvWS where multiple etiologies are present, the treatment can help elucidate the driving cause. We decided to treat our patient with rituximab to target CLL first. In this manner, if rituximab is successful in causing remission of AvWS, then the primary etiology is most likely CLL. However, if rituximab fails, it does not necessarily rule in or rule out either CLL or SMM as the underlying etiology. It may indicate that the patient needs a different set of therapeutic agents other than rituximab monotherapy to treat CLL, or the underlying etiology may be SMM. Our patient responded to rituximab with normalization of FVIII activity, vWF:Ag, and vWF:RCo levels which pointed to CLL as the driver of her AvWS with SMM as the innocent bystander. Even after her AvWS was in remission clinically and by laboratory parameters, the patient's SPEP, light chain ratio, and immunofixation continued to show stable monoclonal gammopathy. This helped establish that SMM was most likely not the underlying etiology of her AvWS. A similar case of confounding etiology was reported by Pardos-Gea et al.[17] In their case, the patient with underlying Sjorgen's syndrome and CLL was diagnosed with AvWS. The patient was first given a five-day course of IVIG to treat the autoimmune condition as the cause of the patient's AvWS. IVIG did not improve the laboratory parameters and bleeding associated with her AvWS. Next the patient's CLL was treated with rituximab and bendamustine, which led to remission of the patient's AvWS. After completion of treatment and remission of AvWS, the patient's autoantibody profile and clinical findings continued to show persistent Sjorgen's syndrome.

Two years after completing her maintenance therapy with rituximab, our patient represented with gum bleeding and relapse of her AvWS, at which point she was treated with obinutuzumab/venetoclax. Hegerova et al did report a case of a patient with AvWS secondary to CLL who underwent several rounds of chemotherapy.[18] The CLL responded to each round of chemotherapy; however, the patient's AvWS continued to be refractory to each treatment. Ultimately the patient underwent allogeneic stem cell transplant for CLL, which caused remission of her AvWS. At the time of this report, our patient was on obinutuzumab/venetoclax for six months with complete alleviation of her bleeding and normalization of FVIII activity, vWF:Ag, and vWF:RCo levels.

LEARNING POINTS

Whenever acquired von Willebrand's syndrome is suspected, it is important to investigate for any underlying myeloproliferative or lymphoproliferative disorder.

In a situation where multiple possible etiologies of AvWS are present, it may be worthwhile to direct the treatment at the most common etiology, and monitor the response rather than targeting multiple etiologies at the same time.

Patient should an integral part of the care as close follow-up is extremely important in monitoring the response to the treatment of AvWS.

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