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Reversal of acquired von Willebrand syndrome with allogeneic stem cell transplant for chronic lymphocytic leukemia

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ABSTRACT

Acquired von Willebrand syndrome (AVWS) is a rare, potentially fatal bleeding disorder caused by low activity of von Willebrand factor (VWF) in patients without congenital deficiency. The majority of adult cases are associated with hematological malignancy, including lymphoproliferative (48%) or myeloproliferative (15%) disorders (Federici et al., 2000). Both qualitative and quantitative defects occur, due to antibody-mediated clearance or functional interference, increased proteolysis, absorption to malignant cells or platelets, or increased shear stress due to valvular defects or mechanical vascular devices (Tiede et al., 2011). The predominant mechanism for decreased or absent VWF in malignancy is autoantibodies that are inhibitory to VWF function or shorten VWF survival (Kumar et al., 2002 [3]). Antibody-mediated clearance occurs through inactivating antibody directed towards VWF, antibody binding the non-active sites of VWF, and nonspecific antibodies that form circulating immune complexes with VWF, enhancing clearance by the reticuloendothelial system (Mannucci et al., 1984). Bleeding may be very difficult to treat due to reduced half-life of VWF-concentrates.

1. Introduction

We describe a case of severe AVWS associated with chronic lymphocytic leukemia (CLL), complicated by suspected Richter's transformation, with resolution of the bleeding disorder after allogeneic hematopoietic cell transplantation (alloHCT). To our knowledge, this is the first reported case of successful alloHCT for a hematologic malignancy complicated by AVWS, without the use of prophylactic VWF-concentrates.

2. Case presentation

A 41 year-old man presented with epistaxis and bruising. He reported prior spine surgery and tooth extraction without bleeding complications and no family history of bleeding. Initial evaluation showed low VWF antigen 31% (VWF:Ag; normal 55–160), VWF ristocetin cofactor activity 29% (VWF:RCo; normal 50–175), and Factor VIII activity 35% (FVIII; normal 60–140) but no therapy was required. He had mild lymphocytosis that was thought to be reactive. Four years later, he was found to have worsening lymphocytosis, after presenting with hematuria that did not respond to desmopressin, and resolved after treatment with VWF concentrate. He was diagnosed with Rai stage I CLL with white blood cells 196×10^9/L (WBC, normal 4.5–10.5 $\times 10^9$/L), mild thrombocytopenia 119×10^9/L (normal 150–450 $\times 10^9$/L), normal baseline immunoglobulin levels, and mild adenopathy. As hematuria is not a typical bleeding pattern associated with low VWF, platelet aggregation was done and showed decreased aggregation to ristocetin consistent with VWD.

At age 49, he underwent tonsillectomy complicated by severe postoperative bleeding requiring 30 units of red blood cells, and prolonged hospitalization. International normalized ratio, activated partial thromboplastin time, and fibrinogen activity were normal while VWF:Ag was 38%; VWF:RCo 12% and FVIII activity 45%. Mixing studies with normal plasma showed no inhibitory effect as measured by VWF:RCo and only a small decrease from expected measurement of VWF:Ag (recovered 48% with expected 56% at 0 h and 49% with

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Table 1
Clinical course and laboratory parameters.

Months from diagnosis	Disease status	Treatment	Disease response	Bleeding complications	VWF:Ag % (55–160%)	VWF:RCo % (50–180%)	FVIII % (55–200%)	Platelets ($\times 10^9$/L) [range]
0	Chronic lymphocytic leukemia diagnosed	None	–	Mild epistaxis	21	–	34	120
48	Splenomegaly, rapid lymphocyte doubling time	Rituximab + Fludarabine × 4	Partial response	Severe epistaxis, hematuria	25	< 10	21	90 [70–110]
66	Fatigue, lymphadenopathy	Rituximab + Bendamustine × 8	Partial response	Mild epistaxis	21	< 10	20	70
108	Fatigue, lymphoadenopathy, recurrent infections	Rituximab + Lenalidomide	Stable lymphadenopathy, decrease lymphocyte count	Mild epistaxis	–	–	–	60 [6–80]
114	Lymphadenopathy	Ibrutinib	Decrease lymphadenopathy, improvement fatigue	Epistaxis, easy bruising	–	–	–	60
144	Hypercalcemia, acute kidney injury, diffuse severe adenopathy, splenomegaly	Rituximab + Cyclophosphamide, Doxorubicin, Vincristine, Prednisone (R-CHOP)	Decrease lymphadenopathy	Mild epistaxis	10	< 10	7	60 [25–110]
156	Stable disease	Allogeneic sibling donor transplant	Decrease lymphadenopathy	None	15	< 19	17	115
157					16	< 19	19	70
158					17	< 19	21	80
160			Complete remission		29	< 19	39	80
161	Complete donor engraftment				141	117	132	74
161.5	Acute graft-versus host disease				206	205	218	80

expected 57% after 1 h of incubation) consistent with a non-neutralizing VWF antibody. Multimer analysis showed decreased high molecular weight multimers (HMWM). He was treated with plasma-derived VWF-concentrate, antifibrinolytics, and desmopressin. One-hour and 15-min post-Humate-P infusion 80 U/kg, VWF:Ag increased to 78%, VWF:RCo to 24% and Factor VIII to 49%. Later he had further VWF half-life testing after 50 U/kg which showed pre-infusion (VWF:Ag 31%, VWF:RCo < 10%, FVIII 42%), 10-min post-infusion (VWF:Ag 145%, VWF:RCo 105%, FVIII 93%), and 3–hours post-infusion (VWF:Ag 71%, VWF:RCo < 10%, FVIII 57%). Pharmacokinetic testing showed normal in vivo recovery, but markedly reduced half-life for both VWF and FVIII, consistent with rapid clearance of VWF due to non-neutralizing autoantibodies. Based on these investigations, he was diagnosed with AVWS due to CLL. He received trial of IVIG 1 g/kg which did not result in meaningful prolongation of VWF half-life (post-IVIG VWF:Ag 20%, VWF:RCo 10%, FVIII 29%).

His CLL progressed and over the next 9 years, he received several courses of chemotherapy, all of which were effective in treating his CLL, but none of which resulted in improvement in VWF levels (Table 1 and Fig. 1A). He had occasional bruising but no bleeding despite periods of chemotherapy-induced thrombocytopenia. He eventually presented with progressive lymphadenopathy, malignant hypercalcemia and acute renal failure. PET/CT showed diffuse adenopathy concerning for Richter's transformation. Bone marrow biopsy was complicated by profuse bleeding despite factor replacement therapy and showed 20–30% involvement with CLL. He declined lymph node biopsy due to high risk for bleeding. Thus, he was empirically treated for suspected transformation to an aggressive lymphoma with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) plus ibrutinib. He achieved partial response after 6 cycles of chemotherapy. Renal dysfunction and hypercalcemia resolved. Despite this aggressive immunosuppression, his AVWS persisted.

He elected to undergo non-myeloablative alloHCT as potentially curative therapy. VWF-concentrate was given prior to and after insertion of a central-venous catheter (CVC) without bleeding complications. He received therapeutic plasma exchange (TPE), and was noted to require lower doses of VWF-concentrate than expected to maintain adequate levels of VWF and FVIII, suggestive of delayed clearance in setting of TPE (Fig. 1B). His bleeding prophylaxis plan in anticipation of transplant-induced thrombocytopenia consisted of TPE for VWF antibody removal on days −19, −16, −14, −12, −9, and −7 prior to alloHCT. TPE transiently improved VWF parameters, but they returned to baseline within 48 h. Transplant was delayed by 25 days due to acute kidney injury and hyperuricemia, presumed secondary to acute tubular necrosis associated with fluid shifts from TPE. With supportive care, his renal function recovered to a baseline creatinine of 1.3 g/dL and he eventually proceeded with 8/8 matched, sibling peripheral blood stem cell transplant (PBSCT). No further TPE was performed due to concern for renal injury.

No bleeding complications were encountered during transplantation and he did not require VWF-concentrates post-alloHCT. Note that sequestered VWF was provided in platelet transfusion support during post-transplant period. Further bone marrow biopsies were deferred due to high bleeding risk. PET/CT at day +106 showed a complete response. Donor engraftment was considered complete (> 95%) at Day +139, with peripheral blood chimerisms showing 98% donor in myeloid and 97% donor in lymphoid fractions (Fig. 1C). This was accompanied by an increase of VWF antigen and activity followed by normalization of VWF parameters at day +154 (day +139 VWF:Ag 29%, VWF:Act < 19% followed by day +154 VWF:Ag 141%, VWF:Act 117%, respectively). He developed late-onset acute GVHD at day +160 [5]. At the time of this report the patient is alive at Day +180, and remains in remission from his AVWS.

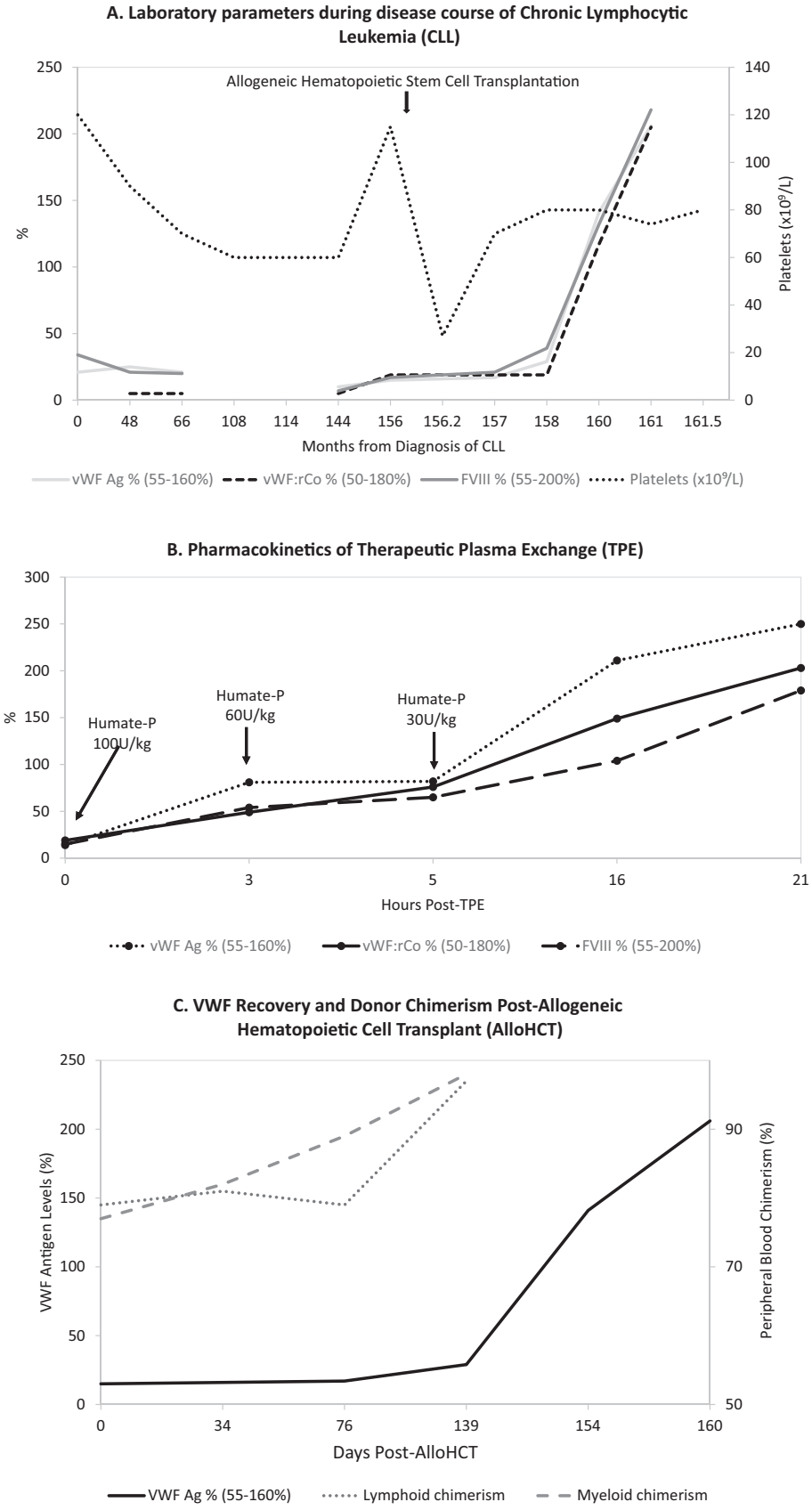

Fig. 1. A. Laboratory parameters during disease course of Chronic Lymphocytic Leukemia (CLL).
B. Pharmacokinetics of Therapeutic Plasma Exchange (TPE).
C. VWF Recovery and Donor Chimerism Post-Allogeneic Hematopoietic Cell Transplant (AlloHCT).

3. Discussion

AVWS should be considered in patients presenting with new-onset mucocutaneous bleeding with no past personal or family history of bleeding. A detailed bleeding history is critical as no one test distinguishes congenital from acquired VWD. Our patient presented in his 40s and had CLL-associated AVWS for nearly 20 years thereafter. Late onset of bleeding without family history should raise suspicion of AVWS; however, a mild inherited VWD can also present in adulthood [2].

Initial diagnostic testing for AVWS is similar to that for inherited VWD, including FVIII activity levels, VWF:Ag, VWF:RCo, and VWF multimer analysis. Other suggested evaluations include echocardiogram to evaluate for valvular disorders and serum protein electrophoresis, complete blood count, and peripheral blood smear to screen for hematologic malignancy [2]. Unlike other antibody mediated bleeding disorders such as acquired hemophilia A, inhibitory antibodies are difficult to detect in AWVS [4]. Therefore, establishing the type and duration of response to desmopressin and/or VWF concentrate to estimate clearance of VWF may help clarify the diagnosis.

Therapy for AVWS is targeted at prevention and treatment of symptomatic bleeding. Perioperative management may include desmopressin and VWF-containing concentrates (although efficacy is limited due accelerated clearance of infused VWF), and antifibrinolytic agents [2,6]. Desmopressin has a reported success rate of only 44% in AVWS associated with lymphoproliferative disorders [1]. Factor VIIa, more commonly used for acquired hemophilia A, has been used for AVWS but caution is recommended given concern for thromboembolic complications [7]. IVIG has been used successfully to treat AVWS, mostly in plasma cell disorders, with higher response rates in IgG type MGUS [2,6] with effect lasting up to 4 weeks. [8,9] Our patient did not respond to IVIG.

In the presence of underlying malignancy, chemotherapy may induce remission of AVWS [2]. However, as illustrated by this case, effective treatment of an underlying malignancy may not always improve AVWS [3]. Our patient's severe bleeding disorder did not improve with treatment for CLL or aggressive lymphoma. It was only after near-complete engraftment post-alloHCT that his VWF antigen and activity increased, and eventually normalized.

AVWS patients undergoing alloHCT are at significant risk of bleeding due to low VWF levels in the setting of mucosal damage from conditioning, prolonged thrombocytopenia, fever, infections, and graft-versus-host disease. Published evidence to guide effective therapies to prevent and treat bleeding with AVWS during alloHCT is lacking.

The only previous published report of alloHCT for malignancy-associated AVWS was in 2004 for a patient with high-risk CLL [10]. Langer et al reported using a continuous infusion of VWF-concentrate from the start of reduced-intensity conditioning until platelet recovery in a patient with severe AVWS with VWF:Ag level of 6% and VWF activity of 2%. No bleeding complications were observed. Similar to our case, normalization of VWF parameters at time of complete donor chimerism occurred.

We instead utilized TPE in an attempt to remove the anti-VWF antibody prior to transplant. TPE has been used to deplete autoantibodies and was beneficial in patients with AVWS associated with IgM-MGUS [8]. Donor plasma instead of albumin should be used as replacement fluid to replace VWF and prevent additional coagulopathy. Our patient had pre-existing CKD from prior chemotherapy and diabetes mellitus, which likely contributed to his acute renal failure exacerbated by TPE. This is to our knowledge, the first report of alloHCT for malignancy-associated AVWS without need for VWF-concentrates. The patient had no significant bleeding episodes prior to or after donor engraftment, with caution taken to avoid invasive procedures such as additional bone marrow biopsies.

We present a case of malignancy-associated AVWS reversed by alloHCT with normalization of both VWF antigen and activity coincident with establishment of complete donor chimerism. AlloHCT can be considered for severe AVWD, particularly in context of malignancy. Further study is needed to better understand AVWS and guide treatment decisions during stem cell transplantation.

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Disclosures

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