Acquired von Willebrand Syndrome Associated With Monoclonal Gammopathy

A Single-Center Study of 36 Patients

Sophie Voisin, MD, Mohamed Hamidou, PhD, Armelle Lefrançois, MD, Marianne Sigaud, MD, Béatrice Mahé, MD, and Marc Trossaërt, PhD

Abstract: In this single-center retrospective study, we evaluated the accuracy of laboratory tests in diagnosing acquired von Willebrand syndrome associated with lymphoproliferative disorders in 36 consecutive patients diagnosed at the University Hospital of Nantes, France. We also compared hemostatic treatments in the following groups: 21 patients with Waldenström macroglobulinemia (WM), 14 with monoclonal gammopathy of undetermined significance (MGUS) (10 with IgG-MGUS and 4 with IgM-MGUS), and 1 with IgA multiple myeloma (IgA-MM). The diagnosis was made in 18 (50%) patients during systematic screening, in 6 (17%) during active mild hemorrhage, and in 12 (33%) during an active, severe bleed. Of the laboratory tests studied, only closure times measured on the Platelet Function Analyzer (PFA)-100 device reliably diagnosed the hemostatic problem. There was no relationship between the factor VIII activity (FVIII:C) or von Willebrand factor activity (VWF:RCo) levels and the previous history of hemorrhage described by patients.

We studied hemostatic treatment in most patients: IgG-MGUS patients responded well to high-dose intravenous immunoglobulin (IVIg) infusions (1 g/kg per d), although patients with IgM-MGUS did not. Desmopressin infusions were effective in 3 patients with IgG-MGUS and 2 patients with IgM-MGUS when the baseline values were above 10 IU/dL, but levels soon returned to the baseline. The 7 WM patients had a good response to desmopressin. These results confirm the efficacy of IVIg in IgG-MGUS patients and the prominent role of closure time in the diagnosis of acquired von Willebrand syndrome.

(*Medicine* 2011;90: 404–411)

Abbreviations: AVWS = acquired von Willebrand syndrome, CT-ADP = closure time test with ADP cartridge, CT-EPI = closure time test with epinephrine cartridge, DDAVP = desmopressin (1-desamino-8-D-arginine vasopressin), FVIII:C = factor VIII activity, ISTH = International Society on Thrombosis and Haemostasis, IVIg = intravenous immunoglobulin, MG = monoclonal gammopathy, MGUS = monoclonal gammopathy of undetermined significance, MM = multiple myeloma, PFA = Platelet Function Analyzer, VWF = von Willebrand factor, VWF:Ag = Von Willebrand factor antigen, VWF:RCo = von Willebrand factor activity, WM = Waldenström macroglobulinemia.

From Laboratoire Hématologie (SV), Centre Hospitalier Universitaire, Hôpital Rangueil, Toulouse; Médecine Interne (MH), Hôtel Dieu, Centre Hospitalier Universitaire, Nantes; Centre Régional de Traitement de l'Hémophilie (AL, MS, MT), Centre Hospitalier Universitaire, Nantes; and Hématologie Clinique (BM), Hôtel Dieu, Centre Hospitalier Universitaire, Nantes; France.

The authors have no funding or conflicts of interest to disclose.

Reprints: Sophie Voisin, MD, Laboratoire Hématologie, Centre Hospitalier Universitaire, Hôpital Rangueil, 1 avenue Jean-Poulhès, Toulouse, France (e-mail: voisin.s@chu-toulouse.fr).

ISSN: 0025-7974
DOI: 10.1097/MD.0b013e3182397166

INTRODUCTION

Acquired von Willebrand syndrome (AVWS) is a rare hemorrhagic disorder that usually occurs in patients with no previous personal or family history of bleeding.[3,37] In about 23% of cases, the bleeding disorder is associated with monoclonal gammopathy (MG).[12] In contrast, to our knowledge there is no report of the prevalence of AVWS in patients with MG. Diagnosis is screened by a prolonged bleeding time or closure time using the Platelet Function Analyzer (PFA)-100 device (Siemens Healthcare Diagnostics, Marburg, Germany), and confirmed by low factor VIII activity (FVIII:C) and low von Willebrand factor activity (VWF:RCo). Patients who have not previously experienced spontaneous bleeding come to medical attention at the time of hemorrhagic complications during invasive procedures.

There are 5 main mechanisms of von Willebrand factor (VWF) deficiency, whereupon VWF is synthesized normally but rapidly cleared from the plasma: 1) inactivation of VWF by specific autoantibodies, 2) formation of immune complexes by nonspecific autoantibodies, 3) absorption of VWF onto malignant cells, 4) increased proteolytic degradation of VWF, and 5) loss of high VWF multimers under high shear stress conditions.[7] The management of AVWS is often difficult, both in terms of controlling bleeding episodes and prophylaxis before surgery or invasive procedures.

Using a database of 59 patients with AVWS, we selected a cohort of 36 (61%) AVWS patients with lymphoproliferative disorders and MG. The other 23 of 59 (39%) patients had AVWS associated with other diseases: 6 with cancer (10%), 5 with chronic myeloproliferative syndromes (9%), 3 with chronic lymphoproliferative leukemia (5%), 4 with cardiovascular disorders (7%), and 5 with miscellaneous diseases (8%). This cohort received diagnosis and follow-up within a single center between 1995 and 2006. We analyzed the clinical and laboratory characteristics of this cohort and the response to different treatments according to the type of lymphoproliferative disorder or monoclonal immunoglobulin. We describe our findings here; awareness of these results could help improve treatment for patients with these hemorrhagic disorders.

PATIENTS AND METHODS

Patients

We retrospectively studied 36 patients with AVWS associated with MG diagnosed between 1995 and 2006. For each patient the MG was classified according to Rajkumar et al.[34] Medical and hemorrhagic histories, such as spontaneous bleeding and postsurgical bleeding, were taken for each patient. Bleeding was considered as both major and active when it was recent, occurring in the last 4 weeks, life-threatening, required medical attention, affected a critical organ (intracranial, retroperitoneal or intraarticular hemorrhage), required a transfusion of at least 2 units of packet red blood cells, or was accompanied by a fall in hemoglobin of >20 g/L. All other bleeding episodes, such

as epistaxis, gingival or gastrointestinal hemorrhage, hematuria, hematomas, and ecchymoses were considered mild. All patients were asked about previous bleeding episodes that occurred before the AVWS diagnosis and during the last 2 years, even if they did not require any further tests, referrals, or treatments at the time.

Laboratory Tests

Venous blood was drawn for laboratory testing using 0.109 mmol/L sodium citrate devices. FVIII:C was measured using a 1-stage clotting assay based on the activated partial thromboplastin time, using FVIII-deficient plasma (STAGO, Asnières, France) and CK Prest reagent (STAGO) on the STA-R system (STAGO). VWF:RCo was assayed using an aggregometer from a commercially available kit (Siemens Healthcare Diagnostics). Von Willebrand factor antigen (VWF:Ag) was measured by enzyme-linked fluorescence on a VIDAS analyzer (Biomerieux, Marcy l'Etoile, France). FVIII:C, VWF:RCo, and VWF:Ag assays were performed in all patients, except for VWF:Ag in the case of 1 patient with IgG-monoclonal gammopathy of undetermined significance (IgG-MGUS). Closure time was determined using the PFA-100 device using both cartridges with either epinephrine (10 μg) (CT-EPI) or ADP (50 mg) (CT-ADP) on the membrane. Venous whole blood was stored at room temperature for less than 4 hours before testing closure time. Closure times were measured in 25 patients: 11 of 21 patients with Waldenström macroglobulinemia (WM), 9 of 10 with IgG-MGUS (1 was screened using only a CT-ADP cartridge, another with only a CT-EPI cartridge), all 4 of the IgM-MGUS patients, and the 1 patient with IgA multiple myeloma (IgA-MM). Bleeding times were measured using a modified Ivy technique with the Simplate sterile disposable apparatus (Organon Teknika Corp., Durham, NC) according to the manufacturer's instructions in 11 patients: 4 of 21 WM patients, 5 of 10 IgG-MGUS patients, 1 of 4 IgM-MGUS patients, and the 1 IgA-MM patient. There was a concerted effort to diagnose all such patients in a uniform manner, but for some patients, AVWS diagnosis occurred during a severe hemorrhagic episode. For those patients, some tests such as closure times were delayed until the hematocrit returned to the normal range. All the assays were performed according to the manufacturers' instructions including standards. Anti-VWF inhibitor screening was evaluated using a Bethesda-derived method on an aggregometer: briefly, normal plasma was mixed with patient plasma at 1:1 vol/vol and incubated for 2 hours at 37°C. The samples were then centrifuged at 2500 g for 15 minutes, and VWF:RCo levels were measured in the supernatants, as previously described.[29]

Therapeutic Trials

We studied the response to the following treatments for both the prevention and treatment of bleeding episodes: intravenous immunoglobulin (IVIg) (Tegeline LFB Biomedicaments, Courtaboeuf, France), desmopressin (DDAVP [1-desamino-8-D-arginine vasopressin], Ferring-SAS, Gentilly, France) and high-purity plasma-derived VWF concentrate with very low factor VIII content (Wilfactin, LFB Biomedicaments). Some patients received daily doses of 1 g/kg IVIg, infused for 2 consecutive days. In these patients, we obtained blood samples before the infusion commenced and then 1, 2, 5, 10, 15, and 20 days later. In some circumstances, patients received other doses (1 g/kg for 1 d, or 0.5 g/kg per d for 4 consecutive d). Concerning desmopressin, the patients were studied in respect of age (aged <75 yr) and in the absence of any cardiovascular antecedents (acute coronary syndromes, stroke, uncontrolled hypertension, deep venous thrombosis, arterial thrombosis). In the absence of any contraindications, DDAVP was infused at a dose of 0.3 μg/kg and blood samples were obtained before and 1, 3, and 6 hours after the infusion began. We systematically evaluated each patient's response by using adapted criteria originally described by Federici et al.[12] The response was considered complete if closure times normalized 1 hour after infusion initiation and both FVIII:C and VWF:RCo levels increased to more than 3 times their baseline values, provided they reach at least 30 IU/dL. For patients undergoing surgical procedures, VWF concentrate was infused using either Wilfactin if FVIII:C >40 IU/dL, or Wilstart if FVIII:C ≤40 IU/dL (both from LFB Biomedicaments, used according to the manufacturer's recommendations). Blood samples were taken before and 1, 2, and 4 hours after the administration of 50 IU/kg VWF concentrate.

RESULTS

AVWS Diagnosis

From a population of 59 patients with AVWS (42 male and 17 female) whose mean age was 59.2 years (extremes, 5.33–100.07), we describe a cohort of 36 (61%) AVWS patients with lymphoproliferative disorders. In these 36 patients (28 male and 8 female; mean age, 63.8 yr; range, 37–91 yr), AVWS was associated with MG: 21 patients with WM, 14 with MGUS (10 IgG-MGUS and 4 IgM-MGUS), and 1 patient with IgA-MM. The kappa light chain was predominant in each group. Patient characteristics are described in Table 1.

Clinical Manifestations

Patients were classified into 3 categories according to the severity of the bleed that led to diagnosis: asymptomatic, mild, or major bleeders (Table 2). Among asymptomatic patients, AVWS was diagnosed during systematic presurgical screening or as part of the diagnostic workup for lymphoproliferative disorder. Eighteen of the 36 (50%) patients were asymptomatic. Six (17%) patients had mild active bleeding or previous hemorrhagic episodes in the last 4 weeks, and the final 12 (33%) were diagnosed during a major active hemorrhage: half of those were spontaneous, 1 followed trauma, and 5 followed surgery. The number of previous bleeds (occurring during the last 2 years) reported was higher in patients who were diagnosed during a bleed; only 3/18 (33%) of the asymptomatic patients and 3/6 (50%) of the mild active bleeding group, but 10/12 (83%) in the major bleeding group reported previous hemorrhagic tendency.

TABLE 1. Population Distribution at Diagnosis

Underlying Disease	No. of Patients	Sex M-F	Age at Diagnosis Mean (Range), yr
WM	21	19–2	63 (37–87)
IgMκ	20		
IgMλ	1		
IgM-MGUS	4	3–1	64 (56–71)
IgMκ	3		
IgMλ	1		
IgG-MGUS	10	5–5	64 (38–91)
IgGκ	9		
IgGλ	1		
IgA-MM	1	1–0	52
IgAλ	1		
Total	36	28–8	64 (37–91)

TABLE 2. Clinical Presentation at Time of Diagnosis

Clinical Presentation by Bleeding Status No. (%)	Diagnosis of AVWS	Previous Bleeding Reported* No. (%)	Laboratory Results No. of Patients/Total Tests (%)	Underlying Gammopathy No. (%)
Asymptomatic (no bleeding): 18 (50)	Systematic screening laboratory testing before surgery or in context of lymphoproliferative disorders	Yes: 3 (17) 1 Mild gum bleeding 2 Bruises No: 15 (83)	Prolonged CT†: 14/14 (100) FVIII:C ≤20 IU/dL: 5/18 (28) VWF:RCo ≤10 IU/dL: 7/18 (39) Both‡: 5/18 (28)	WM: 12 (57) IgM-MGUS: 1 (25) IgG-MGUS: 5 (50)
Mild (active mild bleeding or recent previous bleeding): 6 (17)	Epistaxis (n = 5) Rectal bleeding (n = 1)	Yes: 3 (50) 3 Epistaxis No: 3 (50)	Prolonged CT†: 4/4 (100) FVIII:C ≤20 IU/dL: 0/6 VWF:RCo ≤10 IU/dL: 1/6 (17) Both‡: 0/6	WM: 4 (19) IgM-MGUS: 1 (25) IgA-MM: 1 (100)
Major (major active bleeding): 12 (33)	Gastrointestinal bleeding (n = 2)§ Profuse epistaxis Spontaneous chest hematoma Spontaneous shoulder hemarthrosis¶ Posttraumatic knee hemarthrosis Postoperative bleeding after total hip replacement Thoracic muscle hematoma following pacemaker implantation Post-bone marrow biopsy hematoma Rectal bleeding following endoscopic adenomectomy (n = 2) Bleeding following hysterectomy	Yes: 10 (83) 6 Epistaxis 4 Bruises No: 2 (17)	Prolonged CT†: 7/7 (100) FVIII:C ≤20 IU/dL: 6/12 (50) VWF:RCo ≤10 IU/dL: 8/12 (67) Both‡: 5/12 (42)	WM: 5 (24) IgM-MGUS: 2 (50) IgG-MGUS: 5 (50)
Total			Prolonged CT†: 25/25 (100) FVIII:C ≤20 IU/dL: 11/36 (31) VWF:RCo ≤10 IU/dL: 16/36 (44) Both‡: 10/36 (28)	

Abbreviations: CT = closure time.

*Requiring no additional testing, referral, or visit.

†For most patients, closure times were measured using both cartridges, but for 2 of the IgG-MGUS patients, only 1 cartridge test could be done: 1 was studied with the CT-EPI, and the other with the CT-ADP (see Methods section).

‡Number of patients with FVIII <20 IU/dL and VWF:RCo <10 IU/dL.

§One of these 2 patients (IgM-MGUS) had anti-VWF inhibitor. One IgG-MGUS patient had anti-VWF inhibitor.

¶This patient also had idiopathic thrombopenic purpura (platelets <20 Giga/L).

Laboratory Findings

Closure times were prolonged in all 25 evaluated patients, regardless of clinical presentation and previous bleeding history. Bleeding time was prolonged in 10/11 (91%) patients, but normal in 1 WM patient. Sixteen patients had VWF:RCo ≤10 IU/dL, 9 (56.3%) of whom were bleeders. Eleven patients also had low FVIII:C (≤20 IU/dL), and 6 (54.5%) of them were also bleeders. However, of the 20 patients with VWF:RCo >10 IU/dL and FVIII:C >20 IU/dL, 9 (45%) were bleeders. Considered by MG, the rate of patients with VWF:RCo <10 IU/dL and FVIII:C <20 IU/dL was 80% for IgG-MGUS, 0% for IgM-MGUS, and 5% for WM. The 1 patient with IgA-MM also showed abnormal results, with prolonged bleeding time and closure times and very low levels of FVIII:C and VWF:RCo. We evaluated anti-VWF inhibitor levels in 21 patients (11 WM, 8 IgG-MGUS, and 2 IgM-MGUS). Only 1 IgG-MGUS and 1 IgM-MGUS patient were positive. Both patients experienced severe active bleeding as well as previous bleeds and very low FVIII:C and VWF:RCo levels.

Therapeutic Responses

Intravenous Immunoglobulins

Eight patients, 6 with IgG-MGUS and 2 with IgM-MGUS, received high-dose IVIg treatment (1 g/kg per d for 2 d) (Figure 1). For the IgG-MGUS patients, closure times returned to normal values within the first 2 days, and remained normal for approximately 15 days. As early as day 1, both FVIII:C and VWF:RCo reached normal values, increasing 5 and 14 times above the baseline respectively. The mean values then decreased to <100 IU/dL from day 15. However, in IgM-MGUS patients, this treatment did not improve the laboratory results. Closure times remained prolonged, and either FVIII:C or VWF:RCo remained at <50 IU/dL.

Two IgG-MGUS patients also received different IVIg doses. One was studied after 0.5 g/kg per d for 4 consecutive days and achieved a complete response: FVIII:C and VWF:RCo levels peaked after 5 days and then slowly decreased (data not shown). Closure times also decreased in correlation with VWF:RCo levels' increase. This patient and a second patient also received a single infusion of 1 g/kg IVIg. Only FVIII:C and VWF:RCo levels were measured. Although both patients had nearly the same baseline values, 1 had a very good response, with values >100 IU/dL the following day and a residual peak after 10 days, but the second patient had only a mild increase to 75 IU/dL on day 1, peaking to 100 IU/dL and then decreasing after 4 days. His levels returned to baseline by day 10 (data not shown). The IgA-MM patient also received high-dose immunoglobulin treatment without success: FVIII:C and VWF:RCo levels had not changed by 36 hours postinfusion (data not shown).

Desmopressin

Treatment with desmopressin was evaluated in 13 of 36 (36%) patients: 3 with IgG-MGUS, 2 IgM-MGUS, 7 WM, and the 1 IgA-MM patient (Figure 2). Results are expressed as mean values ± standard deviation for the 4 patient groups. The mean

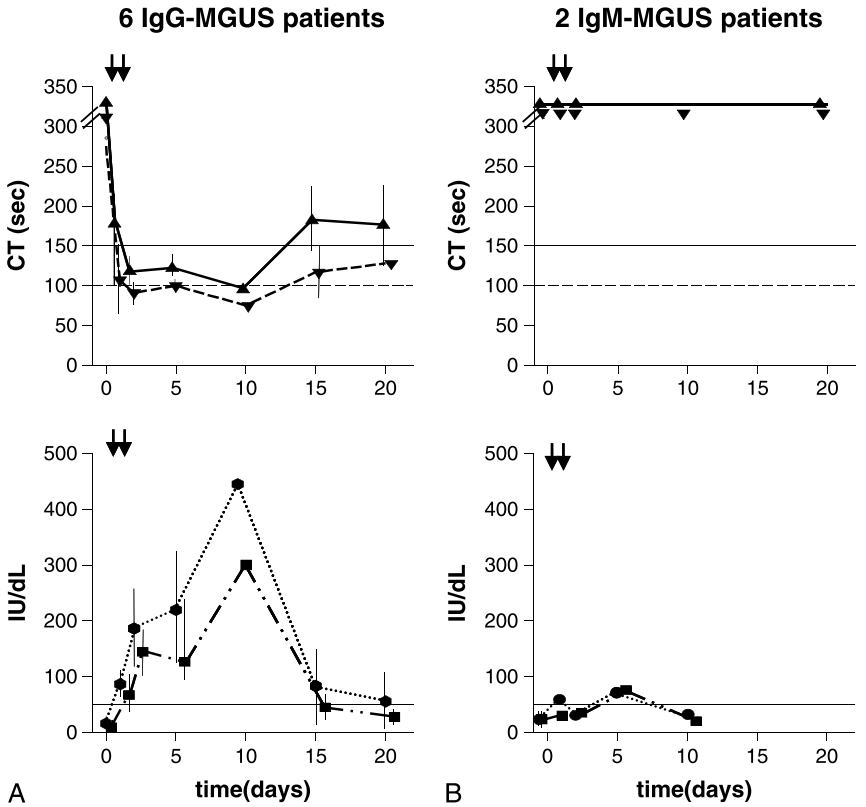

FIGURE 1. Response to high-dose IVIg treatment 1 g/kg for 2 consecutive days in 6 patients with IgG-MGUS (A) and 2 patients with IgM-MGUS (B). Mean values CT-EPI (▲), CT-ADP (▼), FVIII:C (●) and VWF:RCo (■). Results are represented as mean values (solid symbols) and vertical lines showing the intervals ±SD. In some cases the results were obtained for only 1 patient. CT-EPI upper normal limit (—), CT-ADP upper normal limit (– – –), FVIII:C and VWF:RCo lower normal limit (---). CT-EPI = closure time with epinephrine cartridge, CT-ADP = closure time with ADP cartridge.

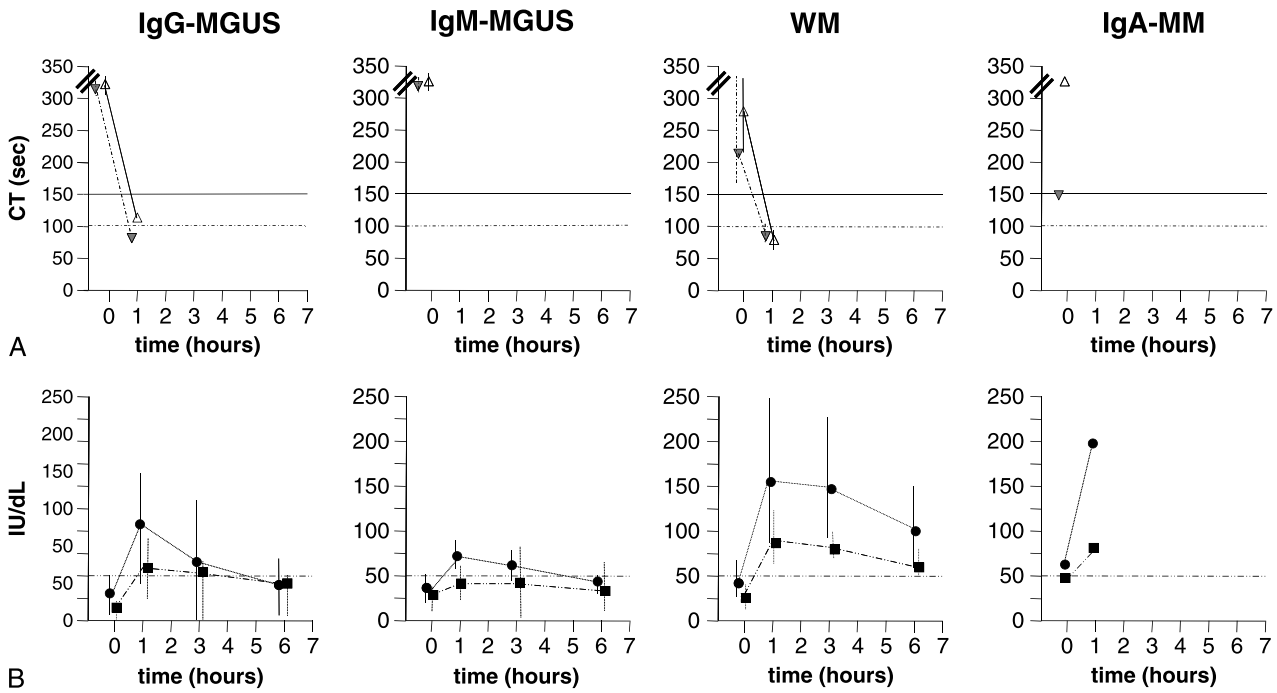

FIGURE 2. DDAVP response to 0.3 μg/kg. Results in 3 IgG-MGUS, 2 IgM-MGUS, 7 WM, and 1 IgA-MM patients. A) Mean values and mean ± SD of CT-EPI (△), CT-ADP (▼), CT-EPI upper normal limit (—), CT-ADP upper normal limit (– – –). B) Mean values and mean ± SD of FVIII:C (●), VWF:RCo (■), FVIII:C and VWF:RCo lower normal limit (---). CT-EPI = closure time with epinephrine cartridge, CT-ADP = closure time with ADP cartridge.

response in the 3 IgG-MGUS patients reached the criteria for a complete response. We could evaluate closure times in only 1 patient because, at the time the other patients had therapeutic evaluation, closure times were not evaluated in our laboratory. In the evaluated patients, values normalized 1 hour (T1) after desmopressin was administered. For the 2 IgG-MGUS patients with baseline FVIII:C and VWF:RCo levels >10 IU/dL, the measurements obtained at T1 satisfied the predetermined criteria. For the last IgG-MGUS patient, who had very low baseline FVIII:C and VWF:RCo levels (5 and 6 IU/dL, respectively), the peaks reached 43 and 19 IU/dL, respectively. Results for the IgM-MGUS patients were incomplete: closure times were measured only at T0. The FVIII:C and VWF:RCo levels showed only a slight increase (2.2- and 1.5-fold, respectively), even though the VWF:RCo peak rose to 42 IU/dL. In both MGUS groups, the half-lives of FVIII:C and VWF:RCo were short, with a return to <50 IU/dL within 6 hours. In the WM group, closure times were measured for 5 patients and both reached normal values by T1. In the WM patients, the FVIII:C and VWF:RCo levels obtained after desmopressin were high and were always >50 IU/dL, even 6 hours after infusion. However, results were considered complete at T1 only in the 5 patients with baseline FVIII:C and VWF:RCo values >20 IU/dL. In the 2 others, with either FVIII:C or VWF:RCo <20 IU/dL, responses were incomplete because the peak did not reach 30 IU/dL. The IgA-MM evaluation was incomplete: closure times were not recorded after desmopressin therapy began, and FVIII:C and VWF:RCo levels were recorded only before and 1 hour after desmopressin infusion, although they showed a good response.

Willebrand Factor Infusions

This treatment was used in 7 patients: 3 with WM, 2 with IgG-MGUS, and 2 with IgM-MGUS. In the WM group, the treatment was effective, with measurements from 2 of the 3 patients showing a FVIII:C and VWF:RCo half-life of greater than 6 hours. In contrast, this treatment was not so effective for the MGUS patients, who needed high-dose infusions (50–80 IU.Kg^{-1}) of factor Willebrand concentrate every 2 or 3 hours to stop severe bleeding (data not shown).

The mean follow-up period for all patients was 6.7 years (range, 0.4–15.8 yr). During the study, no deaths from hemorrhage were observed; 3 WM patients and the 1 IgA-MM patient died from unrelated causes. Three patients (2 WM and 1 IgM-MGUS) received immunosuppressants (chlorambucil, prednisone) without success.

DISCUSSION

According to the literature, AVWS pathogenesis could be explained either by specific autoantibodies that inactivate VWF or by nonspecific autoantibodies that produce circulating immune complexes, with Fc-bearing cells clearing VWF. In some circumstances, VWF could be adsorbed onto malignant cell clones, or its proteolytic degradation could be increased. AVWS is rare, with an estimated prevalence of up to 0.04% in the general population.[23] In the International Society on Thrombosis and Haemostasis (ISTH) database,[9] 186 cases were recorded; most (48%) were associated with a lymphoproliferative disorder, predominantly MGUS (23%). Lymphoproliferative disorders are relatively common causes (30%–48%) of AVWS.[7,11]

In the current retrospective study of 59 consecutive patients with AVWS diagnosed between 1995 and 2006, 36 patients (61%) presented with a lymphoproliferative disorder associated with MG. The majority of patients, that is, 21 (58%), presented with WM, while 14 (39%) had either IgG-MGUS (10 cases) or IgM-MGUS (4 cases). This differs from the ISTH database, where MGUS patients represent the majority (43 of 89 patients,

48%). The prevalence of the kappa light chain is as high in our patients (32 cases, 89%) as it was in previously reported studies.[25,27,44] On the contrary, in the study by Federici et al,[13] lambda light chain prevalence was about 65% in IgG-MGUS associated with AVWS. The male to female ratio was 0.77 in our cohort, higher than the ratio observed in the ISTH database.[9] The mean age at onset was 64 years, in keeping with the ISTH database population,[11] and similar to the results noted in the MGUS and WM populations.[24,26]

For AVWS screening, not all laboratory tests are equivalent. Bleeding time was tested in 11 patients, yet 1 WM patient, who also described recent epistaxis, tested within the normal range. In contrast, closure times measured on the PFA-100 device using either agonist cartridge were prolonged for every patient tested (n = 23). These results strengthen the previously observed high sensitivity of closure time in inherited or acquired von Willebrand disease.[6,16,38] This probably reflects the high sensitivity of closure time on PFA-100 to the loss of high-weight molecular multimers. Unfortunately, multimer studies were not available in the current study. Before any invasive procedure or in cases of active hemorrhage, closure time is the assay of choice to screen for VWF deficiency, especially in patients with lymphoproliferative disorder, where AVWS may be difficult when based only on clinical history.

The FVIII:C and VWF values were usually very low in all but 1 (25%) of the IgM-MGUS group, and 5 (25%) of the WM patients were within the normal range. A 2008 single-center cohort study by Tiede et al[38] estimated FVIII:C and VWF test sensitivity at 64% for AVWS diagnosis. Interestingly, neither FVIII:C nor VWF:RCo levels were lower in bleeders than in asymptomatic patients, so these assays cannot be used to assess the risk of bleeding. Federici et al[13] reported the first study of 10 MGUS patients treated in 2 centers between 1990 and 1996, in which AVWS was diagnosed on the basis of bleeding symptoms and MG (8 with IgG-MGUS and 2 with IgM-MGUS, determined after onset). In that study, all patients had a prolonged bleeding time and low FVIII or VWF:RCo levels, and the relationship between FVIII/VWF measurements and bleeding episodes was reported.[13] Although this information is important to detect the presence of a VWF inhibitor, using this information alone for diagnosis is very difficult. In many cases, the test is negative. Results might be improved by using ELISA assays[35] or collagen-binding techniques[43] instead of ristocetin-mediated interactions.[32] Different techniques for improving detection have been proposed.[2,17,22,32,35,39,41] However, in some cases, discriminating between AVWS and congenital von Willebrand disease remains difficult.[10]

We categorized patients into 3 bleeding patterns, according to the literature. Half (18/36) the patients in our population did not have any active bleeding at the time of diagnosis, and 83% (15/18) of those had no previous history of bleeding. This is lower than in the ISTH database, where 72% of patients reported previous bleeding,[9] probably because diagnosis in the current study was partially assessed through systematic hemostasis screening. The presence of anti-VWF inhibitor does seem to relate to a higher risk of bleeding.[38] Since 50% (n = 18) of the patients in our study were asymptomatic, and 83% of those (n = 15) reported no previous hemorrhage, a simple inquiry is not sufficient to rule out the risk of hemorrhage with invasive procedures. The second half (n = 18) of patients in our study did have active bleeding, two-thirds (n = 12) of whom were considered major bleeders. Most of these patients did report previous hemorrhage. We found no difference in bleeding severity with regard to the type of lymphoproliferative disorder, nor the nature of the monoclonal protein.

Federici et al[13] evaluated 3 hemostatic treatments in MGUS patients and reported that DDAVP and VWF concentrate have very short efficacy in both IgG-MGUS and IgM-MGUS patients.[5,28] The DDAVP response seems to depend on the baseline state of FVIII:C and VWF:RCo; however it could be very effective in WM patients. This treatment, in the absence of any contraindications, requires systematic evaluation to determine its potential efficacy as prophylaxis before invasive procedures and as a treatment option for hemorrhage.

In contrast, IVIg infusions corrected hemostatic abnormalities very effectively in IgG-MGUS patients exclusively for a period of 15-21 days.[13] In IgM-MGUS patients, IVIg is not effective. In the AVWS register,[12] IVIg is more effective in patients with VWF inhibitors.[8,31] For most patients, full-dose IVIg (1 g/kg for 2 consecutive d) is the preferred method for both hemorrhage control and surgical prophylaxis.[13,40,42] For some very responsive patients, low dosages could be suitable for minor surgery or investigative procedures.[20] The mechanisms underlying IVIg's beneficial effects are not fully established, and their efficacy is insufficiently documented.[1,4,15,18,21,33]

Some patients with AVWS in the international register have received immunosuppressive drugs and corticosteroids to treat their underlying disease, with a response in 36% and 32%, respectively.[1,9] In the same way, 3 (2 WM and 1 IgM-MGUS) patients of the current cohort received immunosuppressants (chlorambucil, prednisone), without success. More recently, a monoclonal anti-CD20 antibody, rituximab, has shown some efficacy in treating autoimmune hemorrhagic disorders, such as acquired hemophilia,[14,36,45] and in counteracting autoantibodies in hemophiliac patients. This drug is well tolerated with few complications. Two studies have reported its failure in IgG-MGUS,[19,30] and further studies are needed overall. Its long-term follow-up should be evaluated in AVWS patients.

To our knowledge, the current retrospective, single-center study is the largest single cohort of patients with AVWS associated with MG. As noted in previous studies, the AVWS diagnosis can be difficult since many patients have no or only a slight history of bleeding. However, because of the risk of major bleeding during invasive procedures, diagnosis remains critical. Physicians must be aware of AVWD associated with MG or lymphoproliferative disorder. Clinicians should systematically seek a clinical history of bleeding. In our experience, closure time measured on a PFA-100 device is an easy and very sensitive diagnostic tool. Hemostatic therapy needs to be tested systematically for both treatment and prophylaxis. For patients with IgG-MGUS, IVIg is the treatment of choice. However, as Federici et al[13] previously reported, this treatment seems to be less effective in IgM-MGUS. Desmopressin has a potential role in treatment, particularly if FVIII:C or VWF:RCo baseline values are above 20 IU/dL; further evaluation is required.

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