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CASE REPORT

Diagnosis of congenital von Willebrand disease during a preoperative assessment in a multiple myeloma patient without bleeding history

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Key Clinical Message

We report a rare case of type 2M von Willebrand disease diagnosed in an elderly multiple myeloma patient who had no personal and family bleeding history. This case report emphasis the importance to not systematically exclude a congenital vWD in adult patients when coagulation screening tests indicate toward a vWD.

Keywords

1-desamino-8-d-arginine vasopressin, congenital von Willebrand disease multiple myeloma, preoperative screening, prolonged apTT, von Willebrand factor.

Case Presentation

The case we present concerns a 77-year-old man who was diagnosed in 2008 with an IgA-Kappa MM (10.3 g/L; normal values: 0.7–4 g/L) at a stage III [1]. He was treated with melphalan, corticoids and thalidomide. The patient responded well to the treatment and IgA level decreased to 1.8 g/L. Due to the neurotoxicity side effects of thalidomide, the treatment was changed to dinatrii pamidronas. In 2009, the patient started to develop an osteonecrosis of the jaw, medullar plasma cells were 5%, and IgA levels remained at about 5 g/L for another 3 years. In April 2012, serum IgA went up to 10 g/L and medullar plasma cells rose up to 10%. The patient was further treated with corticosteroids and lenalidomide. IgA level decreased and remained low for another year and a half (2.6 g/L). In October 2013, IgA level was high at 11 g/L and the patient was treated again with lenalidomide in association with corticoids. The treatment lowered IgA level to 4.5 g/L. In April 2014, the patient was admitted to our hospital as he needed surgery for osteonecrosis of the jaw.

In the preoperative coagulation screening tests, an isolated prolonged activated partial thromboplastin time (aPTT) (Synthasil®, Instrumentation Laboratory Company, Bedford, USA) was found with normal platelet count, normal prothrombin time (PT%, Innovin, Siemens Healthcare, Germany), normal thrombin time (TT, Thrombin Reagente, Siemens Healthcare, Germany), and a normal fibrinogen level (Table 1). With no known family and personal histories of bleeding but with a MM-associated hemorrhagic risk, a second analysis and complementary tests were undertaken.

Results suggested an intrinsic coagulation factor deficiency as aPTT was still prolonged using Actin® FS (Siemens Healthcare, Germany), another reagent which is

Table 1. Assessment tests were performed prior to the patient surgery for osteonecrosis of the jaw. First, aPTT, PT, and fibrinogen measurements were done (1st).

Assessment results	1st	2nd	Months after surgery	Normal range
PLT (* $10^3/\mu$L)	233 * 10^3		192 * 10^3	150–440
PT (%)	103.6	101.4	33	>70
INR	0.98	0.98	1.97	0.95–1.31
Fibrinogen (mg/dL)	434	445		200–400
aPTT (s)	34.6	34.1	46.2	21.7–33.9
TT (s)	18.0		16.1	16.2–20.7
Actin® FS (s)	Prolonged			21.3–31.1
Mixing (s)	Normal			21.7–33.9
FVIII (%)	43.6	48.5	67.1	50–200
vWF:Ag (%)	19	20	29	50–200
vWF:RCo (%)	11	13	17.7	50–200
vWF:RCo/vWF:Ag	0.58	0.65	0.61	0.7
FVIII/vWF:Ag	2.29	2.43	2.31	1.0
RIPA (Ristocetin 0.3 ml ml^{-1}) (%)	<10			<10
Collagen-binding Assay (I and III) (%)	39			50–160
vWF:CB/vWF:Ag	2.05			0.7
Multimer analysis	Normal			Detection of a triple structure
Molecular analysis (PCR)	Heterozygous mutation p.R1315C/c.3943C>T in exon 28 of the vWF gene (A1 domain)			No mutation

As aPTT results were perturbed, TT, Actin® FS and mixing analyses were undertaken. Consequent to a prolonged Actin® FS result and corrected mixing study, FVIII, vWF:Ag, and vWF:RCo were evaluated. As the later values obtained were low, vWD was suspected and supplementary tests were done. Samples were sent to UZAntwerpen laboratory for collagen-binding assay, multimer, and molecular analysis. Three days later, low levels of FVIII, vWF:Ag, and vWF:RCo were confirmed on a second sample (2nd). Eight months later, when IgA-Kappa level was confirmed as stable, aPTT, FVIII, vWF:Ag, and vWF:RCo were evaluated to confirm the initial results obtained during the preoperative assessment tests. aPTT (Synthasil, IL), PT (Innovin, Siemens), fibrinogen, TT, Actin® FS (rich is PL), FVIII, vWF:Ag, and vWF:RCo dosage were performed using CS5000 or CS2100 (Sysmex). Finally, RIPA was also performed using Chrono-log Aggregometer.

Platelets (PLT); prothrombin time (PT); activated partial thromboplastin time (aPTT); thrombin time (TT); vWF antigen (vWF:Ag); ristocetin cofactor activity (vWF:RCo); ristocetin-induced platelet aggregation (RIPA).

more sensitive to coagulation factors and less to lupus anticoagulant, and as the prolonged aPTT observed in the screening coagulation tests was corrected by the mixing aPTT study. Further investigations demonstrated decreased levels of FVIII (43.6%) (FACTOR VIII DEFICIENT, Siemens Healthcare, Germany), of vWF antigen (vWF:Ag, Siemens Healthcare, Germany) (19%), and of ristocetin cofactor activity (vWF:RCo, INNOVANCE vWF Ac, Siemens Healthcare, Germany) (11%) (Table 1). The patient's blood group was determined as O positive. The ratios of vWF:RCo/vWF:Ag and FVIII/vWF:Ag were of 0.58 and of 2.29. Finally, the low level in these factors was confirmed 3 days later on a new sample suggesting a vWD.

No inhibitors of FVIII and vWF:Ag could be detected by the Bethesda method suggesting that the decrease in level of these factors were not secondary to auto-antibodies. Electrophoresis of vWF multimer showed a normal triple structure of the protein while collagen (I and III) binding assay was slightly reduced (Table 1). Finally, genetic analysis by PCR was performed and showed a heterozygous mutation p.R1315C/c.3943C>T in exon 28 of the vWF gene which is situated in the domain A1 of vWF protein.

Based on these results and absence of increased platelet aggregation at low ristocetin concentration (RIPA), the DDAVP (1-desamino-8-d-arginine vasopressin) test was evaluated (Fig. 1). FVIII, vWF:Ag, and vWF:RCo were measured 0 min before, 30 and 90 min after, DDAVP injection. The answer was determined as insufficient and led to the administration of recombinant vWF prior to surgery, and of tranexamic acid after his intervention. No bleeding event was recorded.

Eight months after surgery (IgA: 5.3 g/L), the patient was admitted again in our hospital for pyrexia. During his hospitalization, atrial fibrillation was detected and acenocoumarol was administrated. After medication, coagulation tests showed an INR of 1.97 and an aPTT of 46.2 s, probably due to low level of FIX. FVIII level was normal while vWD:Ag and vWD:RCo levels remained low and the vWD:RCo/vWD:Ag ratio was of 0.61 (Table 1). Confirmation of these results several months

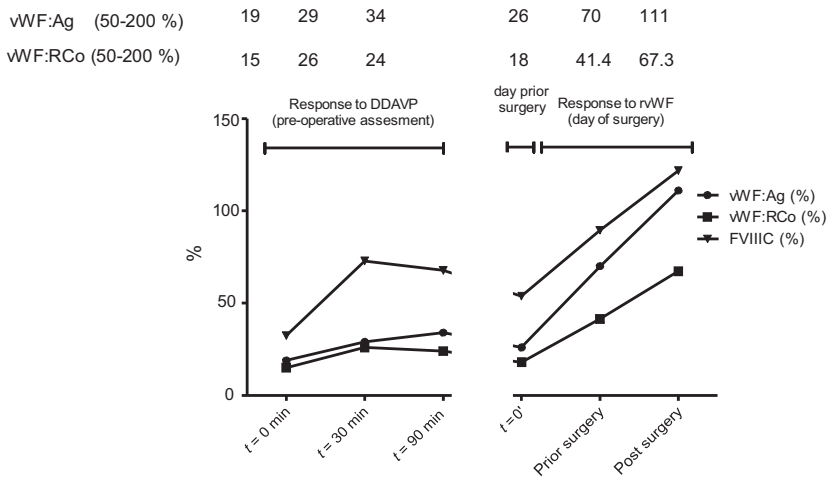

Figure 1. Left side of the graph: FVIII, vWF:Ag, and vWF:Rco were evaluated prior to (t = 0 min) and 30, 90 min after DDAVP administration. As the patient did not respond sufficiently, recombinant vWF was administrated prior to surgery. Right side of the graph: FVIII, vWF:Ag, and vWF:Rco were evaluated prior to recombinant vWF administration and prior surgery (t = 0′), post recombinant vWF administration and prior surgery (*prior surgery*), and post recombinant vWF administration and postsurgery (*post surgery*). There was no hemorrhagic incidence during peri- and postoperation with tranexamic acid. vWF:Ag and vWF:Rco values are situated above the graph. activated partial thromboplastin time (aPTT); vWF antigen (vWF:Ag); ristocetin cofactor activity (vWF:RCo), recombinant vWF (rvWF).

after surgery, in addition to the absence of response to DDAVP, further supports the importance of conducting complete VWF studies in MM patients even if an acquired vWD is suspected in order to avoid hemorrhagic events.

Discussion

vWD is the most commonly inherited bleeding disorder. vWD is either congenital, or more rarely, acquired. Acquired vWD is most frequently observed in MM and it results from the synthesis of new auto-antibodies acting against vWF. The worst case outcome for these patients is hemorrhage during surgery and the clinical picture is usually similar to type II or type I vWD [2].

Three types of congenital vWD have been described and their classification is based on a qualitative or a quantitative default [2]. Type III vWD classification is used for patients with virtually no vWF (<3%) and type I vWD represents patients with an equivalent mild to moderately severe reduction of vWF:Ag and vWF:RCo in the plasma. Type II regroups, all different types of qualitative default in vWF, within which there are four principle subgroups: 2A, 2N, 2M, and 2B [2, 3].

In this case report, we present a patient diagnosed with vWD during a preoperative assessment with a history of MM which was diagnosed 6 years earlier. vWD diagnosis was based on a prolonged aPTT and low levels of FVIII, vWF:Ag, and vWF:RCo. As no auto-antibodies were detected, the hypothesis of an acquired vWD secondary to MM was rejected and the possibility of a congenital vWD was considered.

Patients with an O blood group usually have 25–30% lower levels of vWF than non-O blood group patients and this modestly low vWF level does not predict significant bleeding [4]. In this case report, the patient's blood group was therefore not sufficient to explain a first vWF:Ag value of 19% and a vWF:RCo of 11%. Further tests were then pursued to determine the subtype of vWD in order to avoid any hemorrhagic events during and postsurgery. Indeed, this is important as the treatment of patients with vWD varies with vWD subtypes [3, 5].

The value of the ratio between vWF:RCo and vWF:Ag was not indicative as it defines a gray area which cannot help in discriminating between type I and type II vWD [3]. Collagen-binding protein assay and a ratio vWF:CB/vWF:Ag of 2.05 suggests that the collagen-binding function was not altered. Furthermore, a high FVIII/vWF:Ag ratio (2.3) and the results obtained months after surgery which showed normal levels of FVIII while vWF:Ag remained low, both suggest that vWF synthesis is probably reduced. Of note, while the prolonged aPTT values obtained in the two samples prior surgery were secondary to low FVIII level, the one obtained 8 months after surgery, when FVIII level was back to normal, could be explained by low levels of FIX secondary to acenocoumarol treatment administrated for paroxysmal atrial fibrillation.

No structural default of the protein was revealed and type 2A vWD, which results from a loss of intermediate- and high-molecular weight multimers, was ruled out. As a result of absence of platelet aggregation in response to low concentration of ristocetin (enhanced RIPA) and normal platelet count, type 2B vWD could also be excluded. Finally, as type 2N vWD mutations result in an increased clearance of the factor which is in opposition to the high FVIII/vWF:Ag ratio observed for this patient, this subtype was excluded [5].

The two diagnoses which remain are either a type 1 or a type 2M vWD. Mutation in the A1 domain has previously been reported in type 2M vWD [3]. The distinction is of crucial therapeutic use as most type 2M patients do not benefit from DDAVP treatment due to their loss-of-function phenotype [3, 5].

The heterozygous mutation p.R1315C/c.3943C>T in exon 28 is situated within the A1 domain of vWF monomer which binds to both collagen and platelet GPIb [3, 6]. With a ratio of vWF:CB/vWF:Ag of 2.05, the missense mutation in the A1 domain suggests that it is the binding of vWF to GPIb, rather than to collagen, which is affected by the p.R1315C/c.3943C>T mutation. Even though a reduced production of vWF is suggested by vWF:CB/vWF:Ag and FVIII/vWF:Ag ratio values, the absence of effect of DDAVP on vWF:RCo support that the vWD detected in this case report is a type 2M vWD [6, 7].

Overall, the diagnosis of this patient is probably a type 2M vWD which results from impaired binding of vWF to the platelet GPIb due to missense substitutions in the A1 domain. This could explain the absence of optimal response to DDAVP, ratio vWF:RCo/vWF:Ag < 0.7, normal multimers presence, normal RIPA test, increased ratio FVIII/vWF:Ag > 1.0, and a ratio vWF:CB/vWF:Ag > 0.6. Moreover, type 2M VWD is classically associated with a milder bleeding phenotype than other types of vWD with A1 domain mutation [6].

In conclusion, diagnosis of congenital vWD should always be considered and ruled out prior to surgery, even for an elderly patient diagnosed with MM who presents no personal or family bleeding history. A complete investigation will impact the choice of treatment to avoid perioperative bleeding.

Conflict of Interest

None declared.

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