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CASE REPORT

Perioperative intravenous immunoglobulin treatment in a patient with severe acquired von Willebrand syndrome: case report and review of the literature

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Key Clinical Message

Acquired von Willebrand syndrome may be related to plasma cell dyscrasia and can cause severe bleeding complications. Treatment, for example, with intravenous immunoglobulins may be indicated in selected cases. Physicians treating plasma cell dyscrasia have to be aware of bleeding complications in these patients, and clarification is necessary.

Keywords

Acquired von Willebrand syndrome, bleeding, intravenous immunoglobulins, monoclonal gammopathy of undetermined significance, multimer analysis.

Introduction

Acquired von Willebrand syndrome (AVWS) was first described in 1968 by Simon et al. in a 7-year-old boy with systemic lupus erythematosus [1]. Since this first description, only a few hundred further cases have been known in the literature [2, 3]. AVWS is a rare syndrome that resembles the hereditary form both in terms of clinical signs and laboratory test results, but is not accompanied by a personal or family history of bleeding complications (for review see). In laboratory testing, both forms of the disease may display a prolonged aPTT, a prolonged in vitro bleeding time, a decreased factor VIII: C, a reduced von Willebrand factor (VWF) activity (VWF:RCo), a variable von Willebrand factor antigen (VWF:Ag), as well as often a reduced VWF:RCo/VWF:Ag ratio [4]. By laboratory tests such as plasma mixing assay and measurement of the VWF activity by means of VWF: RCo or ristocetin-induced platelet aggregation, an inhibitor for the VWF is only found in about 16% of patients with AVWS. The VWF multimer analysis is crucial for the diagnosis and may reveal von Willebrand disease (VWD) type 1 or 2A in most of the patients. In order to distinguish the acquired from the hereditary forms of the disease, a detailed medical history regarding bleeding events in the personal and family history is essential.

Several pathophysiologic mechanisms leading to acquired VWF deficiency have been described in the literature [3, 5–11]. Most patients with AVWS produce VWF normally. However, several, mostly immunological processes, promote and accelerate the clearance of VWF. The increased clearance can be induced by antibodies, which happens particularly often in systemic lupus erythematosus [1, 12–14], in monoclonal gammopathy of undetermined significance (MGUS) or multiple myeloma [12, 15–17], and in lymphoplasmacytic lymphoma. These antibodies can be autoantibodies specific to VWF or

nonspecific antibodies forming a circulating complex with VWF. Increased proteolysis of VWF in plasma has been observed in liver cirrhosis, pancreatitis, and leukemia [18] as well as the absorption of VWF by malignant cells, mostly through interaction with GPIb. A loss of large VWF multimers can also be induced by shear stress, especially in cardiovascular disease, artificial heart valves, or myeloproliferative neoplasm (MPN). The use of left ventricular assist devices is often associated with AVWS; this association can be explained by shear stress and increased activity of ADAMTS13 [19]. In MPN, degradation of high molecular weight multimers is most frequently observed [20]. Finally, drug-induced VWF reduction has been observed, for example, after administration of valproic acid, ciprofloxacin, hydroxyethyl starch (HES), and tetracyclines [12]. While absorption of VWF has been described in patients treated with HES, proteolysis of VWF was the mechanism of AVWS in patients treated with ciprofloxacin. In hypothyroidism and after intake of valproic acid, synthesis and release of VWF are reduced [21, 22].

The mechanisms described correlate with the fact that neoplastic diseases play a central role in patients with AVWS: 48% present with a lymphoproliferative disorder, 15% with a myeloproliferative disorder, and 5% suffer from a solid tumor [12, 23, 24]. According to the ISTH registry, MGUS is the most common cause among the lymphoproliferative disorders. Furthermore, cardiovascular disorders have been described in connection with AVWS in about 21% (e.g., congenital and acquired cardiac disease, such as ventricular or atrial defect, aortic valve stenosis, Heyde's syndrome, and ventricular assist devices).

Due to the heterogeneous etiology, as well as the limited number of cases and consequent absence of prospective studies, a standard medical procedure for the treatment and prevention of bleeding complications in AVWS has not yet been developed [23, 25–28]. Treatment options for AVWS include desmopressin (preferred), factor VIII:C/VWF substitution, and activated factor VII (eptacog alfa) for acute bleeding, as well as the application of intravenous immunoglobulins (IVIG) typically acting within a few days [8, 12, 23, 25–27, 29, 30]. Furthermore, long-term treatment includes plasmapheresis, the use of immunosuppressants and antifibrinolytics in monotherapy or in combination.

In the following case report, we describe a patient affected by AVWS related to a smoldering myeloma. We describe the diagnostic workup and the therapeutic decisions with IVIG that have been taken before a surgical intervention AVWS. Written informed consent for the publication of the case report was obtained from the patient reported below.

Case Report

A 75-year-old male presented to our outpatient clinic for evaluation of an increasing tendency to bleed. Von Willebrand syndrome had been suspected in the past because of frequent bleeding throughout the course of approximately 10 years, including prolonged bleeding following a tooth extraction (2004) and massive hematomas after minor trauma, for example, after shaving. The patient's medical history included uneventful tonsillectomy (1962), extraction of nearly all maxillary teeth without increased bleeding tendency (1969), varicose vein operation in the left and right leg with large hematomas (1995), dental extraction with massive secondary bleeding (2004), hemorrhoid sclerotherapy and ligation with severe hemorrhage following release of the ligature (2007), and varicose vein surgery with suture insufficiency (2007). There was no history of bleeding in the patients' family.

Coagulation tests showed a factor VIII:C level of 17%, a VWF:RCo activity of 14%, and a VWF:Ag of 9%, as well as prolonged, immeasurable PFA-100 closure times. A VWF multimer analysis confirmed a pattern compatible with type 2A VWD (Fig. 1). Platelet aggregation was normal after induction with adenosine diphosphate (ADP), epinephrine, or collagen. Furthermore, laboratory workup

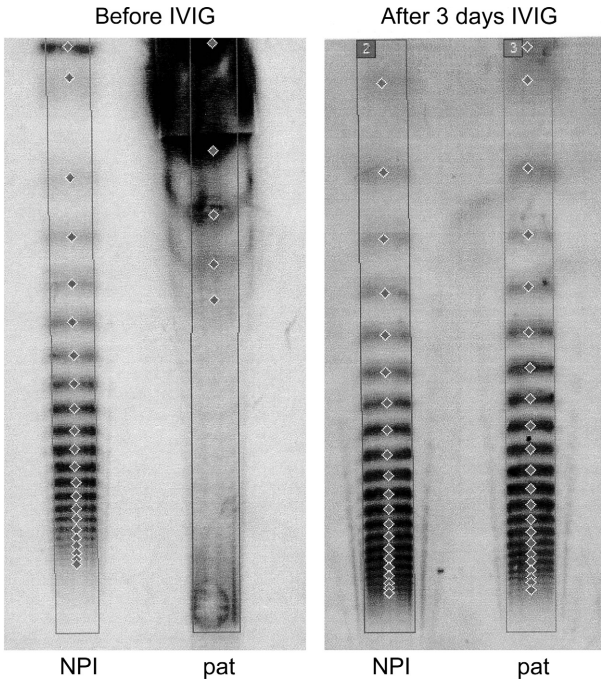

Figure 1. Multimer analysis of the patient showing a type 2A/3 pattern with a globally decreased VWF and with a very low proportion of high molecular weight multimers. The figure shows the multimer analysis before and after 3 days of therapy with IVIG 0.5 g/kg body weight and comparison to a normal subject (NPI) (gel 1.2%).

revealed an IgG kappa type monoclonal gammopathy (M-protein of 0.4 g/dL). In light of the clinical and laboratory findings, AVWS was diagnosed. No further laboratory examinations, such as plasma mixing studies to show an inhibitor or VWF propeptide, were considered necessary for the diagnosis.

For further investigation of the monoclonal gammopathy, an X-ray bone survey and an MRI of the spine were performed, showing no osteolysis or focal lesions. In addition, a bone marrow biopsy was planned, and after the administration of desmopressin, an increase in the VWF activity to 28% was shown which lasted for approximately two hours, thus permitting a bone marrow biopsy without bleeding complications. The patient had no anemia, white blood cell count and platelet count were normal. The bone marrow showed an increase of plasma cells (12%), clinically, CRAB criteria were not present, indicating a stage 1 asymptomatic smoldering multiple myeloma (type IgG kappa), which would not have required treatment by itself. Workup for autoimmune diseases, hypothyroidism, and a drug related AVWS or other AVWS related diseases were excluded.

However, in light of the predisposition for bleeding due to AVWS which was considered life-threatening at this point, systemic treatment of the smoldering myeloma was begun with four cycles of high-dose dexamethasone (40 mg of dexamethasone on day 1–4, 8–11, and 15–18). A mild clinical improvement in the bleeding disorder was observed and was associated with a mild increase in VWF:RCo (from 14% to 22%) and VWF:Ag (from 9% to 21%). In vitro bleeding time was still prolonged but now measurable (229 sec for Coll/Epin and 185 sec for Coll/ADP). However, treatment with dexamethasone was discontinued due to intolerable adverse events, such as weight gain and edema, psychological side effects (insomnia and agitation), and repeated infections. The monoclonal IgG remained stable during the dexamethasone treatment phase.

In a routine screening examination, a basal cell carcinoma of the nose was found that required extended excision with curative intent. A surgical intervention was planned a few weeks later but optimization of the coagulation situation was required before, and the documented short effect of desmopressin was considered insufficient to guarantee optimal bleeding control and wound healing for a period of 3–5 days. Thus, treatment with intravenous immunoglobulins (IVIG) was initiated (0.5 g/kg body weight for 4 days). With this treatment, VWF:RCo, VWF:Ag, and factor VIII:C levels increased to normal levels after 4 days, and this correlated with a decreased bleeding time (Fig. 1). Moderate headaches occurred as an adverse effect of the treatment, which was considered to be meningeal irritation induced by the IVIGs. The surgical intervention was conducted without complications, and wound healing was uneventful. Laboratory examination of the coagulation parameters showed normal values for VWF:Ag and factor VIII:C for approximately 5 weeks after IVIG administration. During this time, the patient received anticoagulation with low molecular weight heparin for permanent atrial fibrillation, which had been known for several years but after the appearance of the AVWS (Fig. 2).

No further treatment for the smoldering myeloma was implemented because bleeding symptoms remained mild (prolonged bleeding after shaving or mild trauma), and no progress of the smoldering myeloma was observed thereafter. The patient continues to be without significant complications after surgery, and without treatment for the smoldering myeloma or AVWS for now 2 years.

Discussion

Our patient was diagnosed with AVWS in late adulthood, after presenting with a bleeding predisposition which he had been suffering from for 10 years. AVWS was ultimately found to be associated with a smoldering myeloma type IgG kappa. The diagnosis of AVWS requires an experienced laboratory with specific testing for VWF parameters, including VWF multimers, and in vivo or in vitro bleeding time. Despite the lack of CRAB criteria, we decided to treat the underlying hematological disease first due to the significant bleeding disorder, and four cycles of dexamethasone were applied. No change in monoclonal IgG was observed, however, clinical surveillance as well as measurement of VWF:RCo and VWF:Ag showed an improvement of bleeding symptoms and some hemostatic parameters during this treatment.

Prior to a planned surgical intervention, treatment with the aim of controlling bleeding complications and permitting optimal wound healing was indicated. At that time, we opted for treatment with IVIG, due to the necessity of a treatment response lasting for at least several days. In patients with VWD, a normalization of hemostasis is recommended for 5 days in case of minor surgery and for 7–10 days for major surgery [31]. We applied the recommended dose of 2 g/kg body weight of IVIG and achieved a normalization of bleeding time, VWF, and factor VIII:C for about 5 weeks.

A response to treatment with IVIG is seen in about one of three patients with AVWS [32–35]. However, the probability of improvement with IVIG is higher in patients with IgG type MGUS (a situation comparable with the IgG smoldering myeloma in this patient) or if an inhibitor to VWF is present [36]. We decided against a treatment with dexamethasone before the basalioma surgery because this treatment had only partially

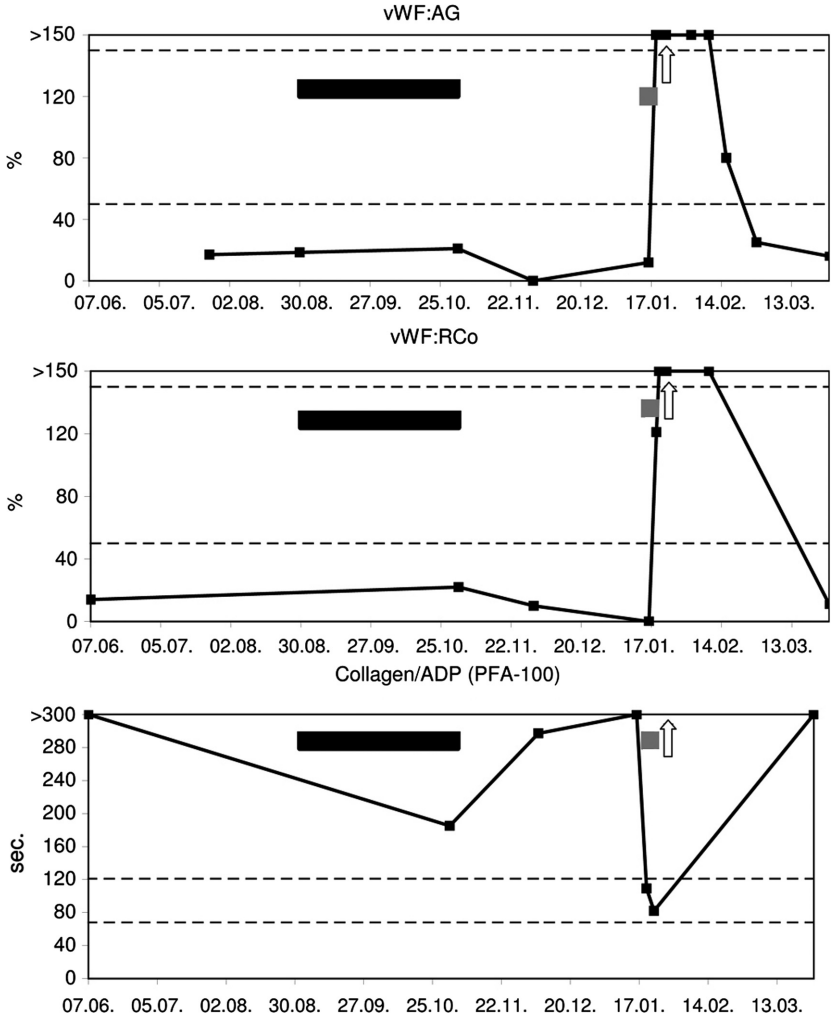

Figure 2. The figure shows the course of VWF:Ag, VWF:RCo, and PFA-100 closure time. The time of treatment with dexamethasone is marked with a black box, the infusion of IVIG is marked with a gray box, and the day of the surgical intervention is marked with an arrow.

improved coagulation parameters previously, and because of multiple infections and other side effects during a previous steroid therapy. As the patient suffered from chronic atrial fibrillation, we speculate that the AVWS protected him potentially against thromboembolic complications without any additional treatment. An effective treatment of the myeloma potentially inducing a remission of AVWS would have triggered an indication for anticoagulation or left atrial appendage occlusion in this patient. Altogether, we decided on a watch-and-wait strategy because the smoldering myeloma was stable, the AVWS caused only mild bleeding complications in daily life and because the patient was very hesitant and anxious about side effects of a treatment.

In case of an acquired bleeding disorder and suspected AVWS, necessary coagulation tests comprise platelet number, platelet aggregation, PFA-100 closure time, factor VIII, VWF:Ag, VWF:RCo, and VWF multimer analysis. Underlying hematological disorders are being explored by a standard blood cell count and microscopical blood smear for myeloproliferative neoplasia; furthermore, patients above 50 years should be searched for monoclonal gammopathy by means of protein electrophoresis and immunofixation [4, 27]. Physicians should be aware of the necessary laboratory tests when bleeding is apparent but also of the necessity to investigate for AVWS in patients suffering from MPN, MGUS, or other diseases related to AVWS, especially when bleeding complications occur or when surgery is planned.

The literature provides several treatment options, but due to the scarcity of robust data, the decision needs to be implemented on a case-by-case basis for most patients [4]. Treatment options differ in their mode and duration of action; when using desmopressin or substitution with

purified VWF, a rapid effect is observed but no more than a short duration of action (about 4 h) should be expected. On the other hand, when intravenous immunoglobulins are used, an effect can only be observed after 2 days, but it will last for up to 3–5 weeks. With regard to treatment using intravenous immunoglobulins, the literature describes a significant difference in the treatment of AVWS between underlying IgG and IgM type MGUS [36]. It could be shown that the use of immunoglobulins had an effect (improvement or normalization of the bleeding time and VWF activity) only in IgG type MGUS, while no effect was seen in IgM type MGUS [4, 17]. The dosage of immunoglobulins, typically 2 g/kg body weight in 2 or 4 days, also appears to have an effect on the response and duration of action *t* [17].

Tranexamic acid is very effective for improvement of epistaxis in AVWS patients, and immunomodulatory drugs (IMIDs) have been proposed as a symptomatic treatment for patients with AVWS-associated gastrointestinal angiodysplasia and bleeding [37].

Acquired von Willebrand syndrome with severe bleeding complications can be an indication for treating a lymphoproliferative or myeloproliferative disorder, even when there is no treatment indication for the hematological disease otherwise. Patients with AVWS and underlying lymphoproliferative disorder seem to have the highest risk of bleeding complications [38]. If the bleeding complications remain mild, a watch-and-wait strategy may be considered. Treatment of the hematological disorder will not always be associated with an improvement of AVWS [39]. The mechanism of AVWS is heterogeneous, even if only patients with a plasma cell dyscrasia (PCD) are considered, and, as a consequence, the response to different treatment options is also unpredictable. Patients with PCD can present with a type 1 or type 2 VWF pattern in multimer electrophoresis but increased fibrinolytic activity or interaction with platelet glycoproteins have also been described [17]. In our patient, dexamethasone had an effect on the coagulation parameters even if a response of the smoldering myeloma was not measurable in the form of a decrease in monoclonal immunoglobulin. Treatment with IVIG was chosen because of the possibility of measuring its effectiveness before surgical interventions, as well as its ability to ensure an adequate coagulation state for the intervention and healing phase due to its prolonged treatment effect. Similar effects of IVIG have also been described in other patients with an underlying IgG monoclonal gammopathy [17, 24]. A significantly shorter effect would have been expected from a treatment with desmopressin, activated factor VII, or purified VWF [30]. Therefore, these treatment options are principally reserved for use in acute bleeding situations, whereas treatment with IVIG can be considered more appropriate for planned interventions because initial response to this treatment takes 2–3 days. IVIG can also be used as a regular infusion every 4 weeks for a long-term effect if treatment of the underlying disease is not possible and bleeding symptoms remain a clinical issue.

In summary, AVWS remains a challenging clinical problem with a difficult diagnostic process and a lack of recommendations for optimal treatment. In patients with myeloproliferative or lymphoproliferative disorders, workup for AVWS is recommended when bleeding signs are observed and prior to surgery. The choice of treatment for AVWS will continue to be decided on a case-to-case basis. The first question to be asked concerns the necessity of treatment of the underlying disease, and the second question concerns the treatment in acute bleeding situation or avoidance of bleeding in predictable risk situation. As prospective studies cannot be expected for this rare and heterogeneous group of syndromes, patients and treatments should continue to be recorded in disease-specific registries to extend our knowledge and allow for appropriate management for various clinical presentations.

Authorship

EJa: performed the treatment of the patient and redaction of the manuscript. DG: corrected the manuscript and referred the physician. AZ: performed the hemostasiology workup with second opinion and correction of the manuscript. LT and THB: corrected the manuscript. SK: involved in the discussion of treatment and correction of the manuscript. EJo: performed the treatment of the patient and redaction of the manuscript.

Conflict of Interest

The authors have no conflict of interests to declare.

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