RESEARCH LETTER

Acquired von Willebrand syndrome during systemic mastocytosis: an analysis of 21 cases

Andrzej Mital, Witold Prejzner, Andrzej Hellmann

Department of Hematology and Transplantology, Medical University of Gdansk, Gdańsk, Poland

Introduction Acquired von Willebrand syndrome (AVWS) is a rare bleeding disorder resulting from von Willebrand factor (VWF) deficiency. Principal factors distinguishing AVWS from the latter condition include lack of prior bleeding disorders, diagnosis at older age, and negative family history. AVWS develops secondarily to other conditions, especially myeloproliferative and lymphoproliferative neoplasms.[1] Mastocytosis is a rare myeloproliferative neoplasm characterized by a monoclonal proliferation of mast cells and enhanced release of their mediators.[2] Recently, an evidence emerged that systemic mastocytosis may be associated with disorders of hemostasis.[3,4] Some mast cell mediators, especially tryptase, heparin, and antithrombin, may act as natural anticoagulants.[5] From the viewpoint of AVWS pathogenesis, the key mediator seems to be heparin, which may bind to VWF and impair platelet adhesion and aggregation.[6] However, limited data on the co-occurrence of AVWS and systemic mastocytosis imply that this problem is of marginal importance.[7,8] Therefore, the aim of this study was to determine the true incidence and clinical implications of AVWS coexisting with systemic mastocytosis.

Patients and methods The study included 21 consecutive patients treated for systemic mastocytosis at the University Clinical Center, Medical University of Gdansk, between 2004 and 2013. The mean (SD) age of patients was 48.0 (14.5) years (range, 26–78 years). The study group included 16 women (76%) and 5 men (24%). The study protocol was approved by the Local Bioethics Committee at the Medical University of Gdansk, and written informed consent was obtained from all participants to use their clinical data for the research purposes. Systemic mastocytosis was diagnosed in line with the current World Health Organization criteria.[9] AVWS was diagnosed on the basis of abnormal activity of the VWF ristocetin cofactor (RCo) (VWF:Rco; reference range, 60%–170%), von Willebrand antigen (VWF:Ag; reference range, 50%–160%), and VWF collagen binding (VWF:CB; reference range, 40%–250%). Furthermore, the VWF:Rco/VWF:Ag and VWF:CB/VWF:Ag ratios (reference ranges ≥0.6) were determined. AVWS was distinguished from hereditary form of von Willebrand disease on the basis of the lack of personal and family history of bleeding disorders.

Statistical analysis Patients with and without concomitant AVWS were compared in terms of their demographic characteristics, laboratory parameters, and previous mastocytosis treatment. The results were analyzed with Statistica 10 package (StatSoft, United States), with the threshold of statistical significance set at a P value of less than 0.05.

Results Among 21 patients with systemic mastocytosis, 8 individuals (38%) had been diagnosed with AVWS (7 women and 1 man). Sex distribution among patients with concomitant AVWS did not differ from that among the remaining 13 subjects with systemic mastocytosis (9 women and 4 men; $P = 0.61$). Moreover, the groups did not differ significantly in terms of age at diagnosis of systemic mastocytosis and age at the time of testing for AVWS (TABLE 1). In 1 patient, AVWS was diagnosed at the same time as systemic mastocytosis; in the remaining patients, clinical and laboratory evidence of AVWS was found 1 year (n = 2), 3 years (n = 3), 6 years (n = 1), and 10 years (n = 1) following the diagnosis of the primary condition. All patients with systemic mastocytosis presented with urticaria pigmentosa type of lesions and carried c-kit D816V mutations. The subset of patients with concomitant systemic mastocytosis and AVWS included 2 persons in whom these 2 conditions co-existed with another disease, polycythemia vera and essential thrombocythemia, respectively. In turn, the subset of patients without

Correspondence to:
Andrzej Mital, MD, PhD, Department of Hematology and Transplantology, Medical University of Gdansk, ul. Dębinki 7, 80-952 Gdańsk, Poland, phone: +48 58 349 22 30, email: amital@wp.pl
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TABLE 1 Demographic and laboratory parameters in patients with systemic mastocytosis with and without concomitant acquired von Willebrand syndrome

Parameter	AVWS (n = 8)		No AVWS (n = 13)		*P* value
	Mean (95% CI)	Range	Mean (95% CI)	Range	
Age at diagnosis of SM, y	46.6 (32.3–60.9)	16–72	43.5 (34.7–52.4)	24–77	0.66
Age at the time of testing for AVWS, y	49.9 (36.2–63.5)	26–78	46.8 (38.4–55.2)	29–78	0.66
Time between SM diagnosis and AVWS testing, y	3.4 (0.7–6.1)	0–10	3.3 (1.7–5.0)	0–10	0.96
EPI closure time, s	203.63 (133.20–274.05)	105–300	140.85 (118.40–163.29)	95–216	0.03
Lactate dehydrogenase, U/l	181.29 (142.23–220.27)	102–230	137.62 (111.76–163.47)	93–259	0.04
VWF:RCo, %	48.75 (40.53–56.97)	38–70	115.62 (90.23–141.00)	66–178	<0.001
Factor VIII, %	97.00 (69.91–124.09)	65–161	114.77 (91.49–138.05)	80–207	0.29
Factor IX, %	106.50 (–14.21 to 227.21)	97–116	101.50 (–6.50 to 209.50)	93–110	0.73
VWF:Ag, %	89.25 (61.42–117.08)	50–138	117.15 (95.96–138.34)	60–165	0.09
VWF:RCo/VWF:Ag ratio	0.61 (0.43–0.78)	0.32–0.88	0.98 (0.88–1.08)	0.65–1.30	<0.001
VWF:CB, %	58.71 (37.65–79.78)	35–90	97.92 (69.01–126.82)	50–192	0.05
VWF:CB/VWF:Ag ratio	0.22 (0.16–0.28)	0.12–0.34	0.15 (0.12–0.17)	0.09–0.23	0.009

Abbreviations: AVWS, acquired von Willebrand syndrome; EPI, epinephrine; SM, systemic mastocytosis; VWF, von Willebrand factor; VWF:Ag, von Willebrand factor antigen; VWF:CB, von Willebrand factor collagen binding; VWF:Rco, von Willebrand factor ristocetin cofactor

AVWS included 1 individual with concomitant thrombocytopenia.

None of the study participants were diagnosed with a myelodysplastic syndrome or were in remission at the time of testing for AVWS. Furthermore, no significant differences were found in the occurrence of splenomegaly between patients with and without concomitant AVWS (1 vs 2, $P = 0.68$), hepatomegaly (0 vs 2, $P = 0.37$), and thrombosis (1 vs 1, $P = 0.63$) at the time of testing. The only significant difference was observed for the signs of bleeding disorders, more frequent in persons diagnosed with concomitant AVWS (6 vs 1, $P = 0.003$). Patients with AVWS were characterized by significantly longer epinephrine closure times and higher concentrations of lactate dehydrogenase than the other patients. Furthermore, they differed from the remaining patients with systemic mastocytosis in terms of most parameters used in the diagnosis of AVWS; specifically, they presented with lower values of the VWF:Rco and VWF:Rco/VWF:Ag ratios, lower VWF:CB, and higher values of VWF:CB/VWF:Ag ratio (TABLE 1). No significant intergroup differences were found in terms of complete blood count parameters, coagulation profiles (except from epinephrine closure times), and concentrations of C-reactive protein and tryptase. Only 3 patients had group 0 which is typically associated with lower plasma levels of VWF.

Clinical presentation in all patients with AVWS was characteristic for disorders of primary hemostasis. Individuals whose manifestations were limited to the skin received etamsylate, and those with epistaxis, vaginal bleeding, or menorrhagia received tranexamic acid and desmopressin. The treatment was effective in all cases. One woman with mast cell leukemia received imatinib at the time of the study (due to lack of typical C-KIT D816V mutation), whereas another patient was treated with hydroxyurea due to concomitant chronic myelomonocytic leukemia. Other patients with mastocytosis did not receive a systemic treatment but were prescribed ranitidine and antihistaminic agents. None of the individuals with mastocytosis were treated with corticosteroids.

Discussion The results presented above imply that AVWS may occur in nearly 40% of patients with systemic mastocytosis. This finding is quite important since available literature data imply that these 2 conditions co-exist only sporadically.[7,8] According to literature, AVWS may result from: 1) formation of specific and nonspecific antibodies that inactivate normally synthesized VWF and enhance its clearance; 2) adsorption of the factor on cancer cells, also resulting in its enhanced clearance; and 3) loss of high-molecular-weight multimers of VWF due to their exposure to elevated shear stress and proteolysis.[1] It cannot be excluded that at least one of these mechanisms contributes to the development of AVWS associated with systemic mastocytosis; however, a relatively higher prevalence of AVWS in persons with this disease than in individuals with other myeloproliferative neoplasms[10] points rather to the presence of a systemic mastocytosis-specific mechanism. The most plausible mechanism leading to a relative deficiency of VWF seems to be blockade of its activity by heparin. This results in adhesion of platelets to glycoprotein GPIb and their aggregation.[6] Moreover, it should be remembered that the blockade of VWF by heparin may exacerbate the course of bleeding disorders occurring in individuals with absolute deficiency of this factor.[7]

The relatively frequent co-occurrence of AVWS and systemic mastocytosis may have significant clinical implications. Firstly, it justifies the inclusion of coagulation tests as part of routine

evaluation of patients with systemic mastocytosis. Secondly, both previous reports on potential mechanisms leading to the development of bleeding disorders in individuals with systemic mastocytosis[7] and our clinical observations imply that routine interventions aimed at restoration of hemostasis, such as administration of vitamin K, frozen plasma, or platelets, are inefficient in the case of AVWS. A more reasonable option seems to be a deactivation of the coagulation inhibitors released by clonal mastocytes, not only heparin, which is likely involved in the pathogenesis of AVWS, but also tryptase and antithrombin responsible for impairment of the coagulation cascade. One solution is administration of corticosteroids during exacerbation of systemic mastocytosis (associated with enhanced mastocyte degranulation).[7] Another important clinical objective should be identification of patients with systemic mastocytosis who are at increased risk of AVWS. This is quite important since a large proportion of patients with systemic mastocytosis are not treated at specialized hematology centers but are managed by other specialists. However, identification of risk factors for AVWS associated with systemic mastocytosis is challenging due to small number of patients with these 2 conditions. The fact that the most plausible mechanism leading to the development of AVWS associated with systemic mastocytosis is blockade of VWF by heparin points to individuals with a particularly severe course of the primary condition as a group at risk.[7] However, also this hypothesis needs to be verified in a clinical setting; due to low incidence of both systemic mastocytosis and AVWS, the only option to accurately identify the risk factors for their co-occurrence seems to be a multicenter trial or cumulative analysis of data from national registries.

One should consider potential methodological limitations of this study which are primarily related to its retrospective design. Some patients with systemic mastocytosis were referred to our center with an already established diagnosis of this condition or due to signs of bleeding disorder, and therefore their medical histories might have been incomplete. Moreover, it cannot be excluded that due to potential selection bias related to the fact that we analyzed solely the patients who have been treated at a tertiary center, the presented findings (especially the data on co-occurrence of AVWS and systemic mastocytosis) cannot be generalized to the whole population of patients with this myeloproliferative neoplasm. Finally, due to retrospective design of our analysis, we were also unable to conclude on a direction of all the reported relationships. However, despite these potential limitations, the presented analysis is, to the best of our knowledge, the largest study on coexistence of AVWS and systemic mastocytosis published thus far.

In conclusion, this study showed that AVWS may develop in approximately 40% of patients with systemic mastocytosis. Consequently, all patients diagnosed with this condition should be routinely tested for hemostatic disorders, including VWF deficiency.

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