

Acquired Von Willebrand Syndrome following a SARS-CoV2 Infection

Michael Iarossi Cedric Hermans

Haemostasis and Thrombosis Unit, Division of Haematology, Saint-Luc University Hospital, Université catholique de Louvain (UCLouvain), Brussels, Belgium

Keywords

Acquired von Willebrand Syndrome · SARS-CoV2 infection

Abstract

Acquired von Willebrand syndrome is a rare clinical entity with approximately 700 cases described in the literature. Different etiologies can be responsible for the occurrence of this condition, including mainly lymphoproliferative and myeloproliferative syndromes, as well as cardiac diseases. Several mechanisms have been implicated depending on the etiology. Viral infections are an extremely rare cause, with only one case reported after an Epstein-Barr virus infection. In this case report, we have described the very likely association between SARS-CoV2 infection and the development of a time-limited acquired von Willebrand syndrome.

© 2023 S. Karger AG, Basel

Introduction

Acquired von Willebrand syndrome (AvWS) is a rare condition, which was first described in 1968 in a young boy with a systemic lupus erythematosus [1]. Its prevalence is difficult to predict, with only 700 cases reported in the literature. It is estimated that 1 in 40 patients referred for a bleeding tendency will be diagnosed with AvWS [2]. AvWS is probably underestimated, given its wide range of clinical features [3]. It is, above all, a pathol-

ogy of the elderly, with the patient's median age being 62 years. Its prevalence is likely on the rise, especially on account of the aging population and given the overall context of increasing predisposing cardiac pathologies [4]. The clinical symptoms are similar to those associated with the inherited form of von Willebrand disease. Several mechanisms may be responsible for an AvWS, including neutralizing or non-neutralizing antibodies, cellular uptake, as well as increased proteolysis or decreased synthesis of von Willebrand factor [5]. Different underlying pathologies can explain the development of AvWS, such as lymphoproliferative, myeloproliferative, autoimmune diseases, solid cancers, as well as cardiological pathologies [6]. The treatment must, therefore, be guided by the underlying pathology. Herein, we have reported a patient with a previously unreported AvWS, which was likely caused by SARS-CoV2 infection.

Case Description

A 27-year-old patient was referred for a suspected von Willebrand disease, following a bleeding work-up initiated by the recent onset of bleeding symptoms. At the end of February 2022, the patient was diagnosed with a SARS-CoV2 infection and positive polymerase chain reaction test, while he was rather paucisymptomatic. Over the following weeks, he developed recurrent bruising, as well as epistaxis and gum bleeds. He was then admitted to the emergency department due to repeated episodes of hematemesis. A gastroscopy did not reveal any lesions. Factor VIII coagulant activity was 18% (normal range, 50–150%), von Willebrand factor

Table 1. Evolution of biological parameters

Assays	3 weeks after infection	6 weeks after infection	12 weeks after infection
vWF:Ag (%)	11	97	86
vWF:RCo (%)	6	89	77
vWF:RCo/vWF Ag ratio	0.54	0.9	0.89
FVIII:C (one-stage assay) (%)	8	108	73
Platelet count ($10^3/\mu\text{L}$)	212	192	214

antigen 11% (normal range, 50–120%), and von Willebrand factor ristocetin co-factor activity 6% (normal range, 50–150%). In April 2022, the patient was referred to the hematology consultation of a tertiary hospital for further work-up. He did not report having experienced any similar symptoms during his childhood, including after hemostatic challenges. He was otherwise completely asymptomatic. The patient's history included a right knee osteotomy in 2019 and tonsillectomy in childhood, each time without any bleeding complications being reported by the patient. There was no family history of bleeding, nor was there any evidence of drug use, whether chronically or as part of the recent SARS-CoV2 infection. He was vaccinated against COVID-19, each time using Pfizer-BioNTech mRNA vaccine (BNT162b2 mRNA), in May, June, and December 2021. The clinical examination was unremarkable. A repeated blood test confirmed an unremarkable blood count with a hemoglobin of 16.4 g/dL (normal range, 13.3–16.7 g/dL), white blood cell count of 6,270/ μL (normal range, 4,000–10,000 / μL), and platelet count of 192,000/ μL (normal range, 150,000–450,000/ μL). Blood flow cytometry did not show a clonality, and protein electrophoresis was normal. Hepatitis A/B/C, cytomegalovirus, Epstein-Barr virus, and human immunodeficiency virus serologies were negative. Chest X-ray revealed neither mediastinal adenopathy nor cardiomegaly. After the most common causes were ruled out, we similarly excluded less commonly reported conditions, such as autoimmune diseases (antinuclear antibodies and rheumatoid factor were negative), sarcoidosis (normal angiotensin-converting enzyme), hemolytic anemia (normal haptoglobin/lactate dehydrogenase), hypothyroidism (normal thyroid-stimulating hormone), diabetes (normal glycated hemoglobin), and renal failure. Surprisingly, at the time of this work-up, the patient did not report bleeding symptoms. Platelet function assay-ADP was 86 s (normal range, 62–100 s), platelet function assay-epinephrine was 147 s (normal range, 82–150 s), factor VIII coagulant activity was 112%, von Willebrand factor antigen was 97%, and von Willebrand factor ristocetin co-factor activity was 89% (Table 1).

Discussion

AvWS is a rare but widespread condition. The occurrence of a mucocutaneous hemorrhagic syndrome in adulthood often leads to a suspicion, although up to 30% of patients are asymptomatic [7], which can, therefore,

explain its under-reporting. The symptoms are similar to those of hereditary von Willebrand syndrome, ranging from minor to moderately severe bleedings, such as bruising, epistaxis, gum bleedings, or gastrointestinal bleeding. The mechanisms are multiple, depending on the underlying pathology found, such as neutralizing or non-neutralizing antibodies, cellular uptake, as well as increased proteolysis or decreased synthesis of von Willebrand factor [6]. The biological picture is most often suggestive of type 2 von Willebrand syndrome, but all types have been described in the literature. Historically, hematological malignancy was the main cause of AvWS, including lymphoproliferative syndromes (48%) and myeloproliferative syndromes (15%), together with monoclonal gammopathy of undetermined significance, myeloma, Waldenström macroglobulinemia, chronic lymphocytic leukemia, non-Hodgkin's lymphoma, essential thrombocythemia, Vaquez disease, chronic myeloid leukemia, and myelofibrosis. Next in order of frequency are cardiovascular diseases (21%), such as aortic stenosis, left ventricular assist device, extracorporeal membrane oxygenation, endocarditis, ventricular/atrial septal defects, which are likely more preponderant in new registers [4, 7]. In the following, we find autoimmune pathologies (systemic lupus erythematosus, scleroderma, or mixed connective tissue), with solid cancers, such as Wilms tumor, primitive neuroectodermal tumors, adrenocortical carcinoma, lung carcinoma, or gastric carcinoma, also reported. Finally, various other clinical entities have been described including drug use (ciprofloxacin or valproic acid), hypothyroidism, diabetes, renal insufficiency, sarcoidosis, as well as others [8]. The diagnosis should be suspected in the presence of a new bleeding diathesis in an adult without any family history of bleeding disease. Once confirmed, an etiological assessment is recommended for proper disease management. In case of doubt, a genetic analysis is recommended to help with the diagnosis, while avoiding

to incriminate a secondary cause, which is often only incidentally present [4]. The mechanism behind AvWS due to a viral infection is not clearly understood, given that it is a very rare cause, which has, therefore, been little investigated. It can be hypothesized that the development of antibodies following infection constitutes the suspected pathological mechanism. SARS-CoV2 infection is associated with multiple clinical manifestations, including autoimmune diseases associated with antibody production. Indeed, in patients hospitalized with SARS-CoV2 infection, a study demonstrated that autoantibodies targeting traditional autoantigens or cytokines do develop *de novo* in 50% of patients, most often only transiently [9].

Self-resolving AvWS has not often been reported in the literature, as it is commonly associated with chronic disease. Moreover, only treatment of the underlying disease will likely lead to resolution of the syndrome. However, assuming transient antibody production as secondary to viral infection, spontaneous favorable evolution appears possible. In the literature, one case of AvWS related to an infectious cause has been reported in a 6-year-old child who developed a hemorrhagic diathesis following Epstein-Barr virus infection [10]. Similar to our case, the symptomatology was moderate and relatively brief, with complete symptom disappearance within a few weeks.

Our case highlights an atypical presentation of a young man with no notable history of hemorrhagic symptoms, in spite of two hemostatic challenges, yet without any complications. He developed symptoms that were suggestive of an acquired bleeding diathesis, with an initial work-up in favor of a type 2 vWS. Yet, at the time he was admitted to the hematology clinic, the bleeding symptoms had already resolved, and the control blood tests were no longer showing any abnormalities. Obviously, we are not in the position to establish a formal causal link between SARS-CoV2 infection and vWS, which occurred at a time of high endemicity of COVID-19. Nevertheless, our work-up did not enable us to identify any of the other etiologies reported in the literature. Finally, it should be remembered that a minority of AvWS are idiopathic, though the favorable evolution of our patient did not favor this possibility.

As illustrated by the above-described case and our observations, the diagnosis of AvWS is possibly underestimated, given that the symptomatology is usually moderate, while the syndrome does not persist over time. Our case illustrates the possibility of an AvWS developing following a viral infection, such as a SARS-CoV2 infection,

in a temporary manner, with a complete regression of the symptoms and resolution of laboratory abnormalities within several weeks.

Conclusion

AvWS is a well-known clinical entity with numerous etiologies, with a most likely underestimated prevalence. Herein, we have reported a case of AvWS, which was likely caused by SARS-CoV2 infection, exhibiting a rapidly favorable evolution.

Statement of Ethics

Ethical approval was not required for this case report in accordance with local or national guidelines. Nevertheless, written informed consent was obtained from the patient for publishing the details of his medical case.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This case report was written in the absence of any funding.

Author Contributions

The patient was seen in consultation by Prof. Cedric Hermans for the initial assessment, while the follow-up was conducted by Dr. Michael Iarossi. The article was written by Dr. Michael Iarossi and corrected by Prof. Cedric Hermans.

Data Availability Statement

All data generated or analyzed during this study were included in this article. Further inquiries can be directed to the corresponding author.

References

- 1 Simone JV, Cornet JA, Abildgaard CF. Acquired von Willebrand's syndrome in systemic lupus erythematosus. *Blood*. 1968;31(6): 806–12.
- 2 Tiede A. Diagnosis and treatment of acquired von Willebrand syndrome. *Thromb Res*. 2012;130(Suppl 2):S2–6.
- 3 Budde U, Bergmann F, Michiels JJ. Acquired von Willebrand syndrome: experience from 2 years in a single laboratory compared with data from the literature and an International Registry. *Semin Thromb Hemost*. 2002;28(2): 227–38.
- 4 Tiede A, Rand JH, Budde U, Ganser A, Federici AB. How I treat the acquired von Willebrand syndrome. *Blood*. 2011;117(25):6777–85.
- 5 Tiede A, Priesack J, Werwitzke S, Bohlmann K, Oortwijn B, Lenting P, et al. Diagnostic workup of patients with acquired von Willebrand syndrome: a retrospective single-centre cohort study. *J Thromb Haemost*. 2008; 6(4):569–76.
- 6 Franchini M, Mannucci PM. Acquired von Willebrand syndrome: focused for hematologists. *Haematologica*. 2020;105(8):2032–7.
- 7 Rand J, van Genderen P, Bucciarelli P, Budde U, Meyer D, Mohri H, et al. Acquired von Willebrand syndrome: data from an international registry. *Thromb Haemost*. 2000; 84(08):345–9.
- 8 Kumar S, Pruthi RK, Nichols WL. Acquired von Willebrand disease. *Mayo Clin Proc*. 2002;77(2):181–7.
- 9 Chang SE, Feng A, Meng W, Apostolidis SA, Mack E, Artandi M, et al. New-onset IgG autoantibodies in hospitalized patients with COVID-19. *Nat Commun*. 2021;12(1):5417.
- 10 Kinoshita S, Yoshioka K, Kasahara M, Takamiya O. Acquired von Willebrand disease after Epstein-Barr virus infection. *J Pediatr*. 1991;119(4):595–8.