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# Digestive Angiodysplasia Revealing Acquired Type 3 Von Willebrand Syndrome Associated with MGUS: A Case Report

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**Abstract** **Case Report**

While congenital von Willebrand disease is common and usually diagnosed early, acquired von Willebrand syndrome (AVWS) remains a rare and often underestimated cause of bleeding disorders in elderly patients. It typically occurs in the absence of personal or family history of bleeding and is most often associated with an underlying condition. The clinical presentation of AVWS is polymorphic, predominantly involving mucocutaneous or gastrointestinal manifestations. Gastrointestinal bleeding, frequently related to angiodysplasias, may be chronic or recurrent and represents a major cause of iron-deficiency anemia and prolonged diagnostic delay. This clinical variability explains the frequent delay in disease identification. Diagnosis relies on a combination of clinical and biological findings demonstrating a deficiency of von Willebrand factor, impaired functional activity, and reduced factor VIII levels. Etiological investigation is essential for appropriate therapeutic management. Severe forms, related to type 3 deficiency, expose patients to potentially life-threatening spontaneous bleeding. Management primarily relies on treatment of the underlying causal condition, which is the only approach capable of achieving sustained improvement in hemorrhagic manifestations. Early recognition of AVWS, particularly in the presence of unexplained angiodysplasias, significantly improves patient prognosis.

**Keywords:** Angiodyplasia, Type 3 deficiency, Acquired von Willebrand syndrome (AVWS), Monoclonal gammopathy.



## INTRODUCTION

Von Willebrand factor (vWF) is a glycoprotein synthesized by endothelial cells and megakaryocytes, playing an essential role in primary hemostasis. vWF abnormalities can be constitutional, defining von Willebrand disease, or acquired, corresponding to acquired von Willebrand syndrome (AVWS).[1], [2]

AWS is a rare and often underdiagnosed bleeding disorder that usually occurs in elderly patients with no personal or family history of bleeding. It is frequently associated with underlying conditions, including lymphoproliferative disorders, such as monoclonal gammopathy of undetermined significance (MGUS), which is part of the monoclonal gammopathies of clinical significance (MGCS), myeloproliferative neoplasms, and certain cardiovascular diseases. [3] [4], [5]

We report a case of acquired type 3 von Willebrand syndrome secondary to MGUS, revealed by recurrent gastrointestinal bleeding associated with a long-standing angiodysplasia. This rare presentation illustrates the diagnostic challenges of AVWS in elderly patients and emphasizes the need to investigate underlying conditions such as monoclonal gammopathies to guide effective management

## CASE REPORT

We present the case of a 76-year-old female patient being treated for hypertension with beta-blockers and with no other medical or surgical history. Upon

questioning, no personal or family history of hemorrhage was found.

The patient was managed at Mohamed V Military Instruction Hospital and consent was obtained from the patient for publication of this case report.

The history of the disease dates back to ten years , marked by several episodes of gastrointestinal bleeding, including profuse rectal bleeding and melena, which led to numerous hospitalizations. The patient underwent several investigations and treatments, including arteriography with embolization, without any significant clinical improvement.

The course of the disease was then characterized by the onset of severe anemia, requiring repeated blood transfusions, associated with a progressive deterioration in her general condition.

During her last hospitalization, an enteroscopy revealed multiple lesions of small intestinal angiodysplasia. As part of the etiological investigation of these lesions, a hemostasis assessment was performed, in addition to routine biological tests, including a complete blood count.

The blood count results revealed microcytic hypochromic anemia, with hemoglobin at 5.9 g/dL, MCV at 70.5 fL, and MCHC at 26.7 g/dL. Platelet and white blood cell counts were normal, at 321,000/mm³ and 3,500/µL, respectively.

Hemostasis testing showed prolonged activated partial thromboplastin time (APTT), with a ratio of 1.5 (patient APTT 53 vs. control 36 s), associated with normal prothrombin levels (PT 100%). It revealed a severe von Willebrand factor deficiency, with von Willebrand factor antigen (vWF:Ag) at 3% and activity (vWF:Ac) < 15%, associated with a marked decrease in factor VIII to 3%. The absence of circulating anticoagulants was confirmed. The levels of other coagulation factors were normal, including factor V at 148%, factor IX at 92%, and factor XI at 89%. The fibrinogen level was 4.4 g/L.

Thus, a biological diagnosis of type 3 von Willebrand syndrome was made, due to the collapse of FvW:Ag and factor VIII levels. The von Willebrand factor propeptide assay, which is useful for confirming the acquired nature of the disease, was not performed because the test was not available at our center. However, the acquired nature of the disease was suggested by the absence of a personal or family history of bleeding and the late onset of bleeding signs.

In the context of etiological research into acquired von Willebrand disease, no medication or toxic substances were found during questioning, echocardiography to check for heart disease was normal, a CT scan of the neck, chest, abdomen, and pelvis showed no evidence of tumor syndrome, immunological testing for antinuclear antibodies, rheumatoid factor, and antiphospholipid antibodies was negative, thyroid function is normal, blood smear did not reveal any atypical cells, however, serum protein electrophoresis (SPE) revealed a double peak migrating in the gamma globulin zone, quantified at 5.7 g/L, IgG kappa isotype on serum immunofixation, serum free light chain assay found a Kappa FLC level of 24.94 and a Lambda FLC level of 15.02 with an abnormal K/L ratio of 1.66. Monoclonal gammopathy was thus identified.

In the absence of renal failure, hypercalcemia, and bone lesions in our patient, the diagnosis was acquired von Willebrand syndrome (SVWA) secondary to clinically significant monoclonal gammopathy (MGCS). The patient is being treated with tranexamic acid combined with targeted treatment of the monoclonal clone using a combination of thalidomide and dexamethasone, with monthly clinical and biological assessments.

## DISCUSSION

Acquired von Willebrand syndrome (AVWS) is a rare hemorrhagic disorder characterized by abnormalities of von Willebrand factor (vWF) similar to those observed in congenital von Willebrand disease, but occurring secondary to an underlying condition. It predominantly affects elderly patients with no personal or family history of bleeding [2].

Since its first description in 1968, approximately 300 cases have been reported in the literature, highlighting the exceptional rarity of this condition [1,2,4].

The hemorrhagic manifestations of AVWS are variable, ranging from postoperative bleeding to occult hemorrhage responsible for prolonged diagnostic delay. These heterogeneous clinical presentations explain the diagnostic difficulty and the frequent delay in appropriate management [6].

AVWS is often associated with an underlying disorder that is not always identified. Etiologies are diverse and include lymphoproliferative disorders such as monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma, Waldenström macroglobulinemia, and non-Hodgkin lymphoma, as well as myeloproliferative neoplasms such as essential thrombocythemia and certain cardiac diseases [4]. In our case, AVWS was most likely secondary to MGUS, fitting within the spectrum of monoclonal gammopathy of clinical significance (MGCS).

The differential diagnosis with congenital von Willebrand disease must be systematically considered, as therapeutic management differs. Three main arguments support the diagnosis of AVWS: absence of personal or

family history of bleeding, the presence or discovery of an associated underlying condition, and resolution of hemorrhagic symptoms after treatment of the causal disease when feasible [6].

Thus, MGUS may rarely be complicated by AVWS, giving rise to the concept of monoclonal gammopathy of clinical significance (MGCS), a symptomatic entity lacking the criteria of disease progression that define multiple myeloma [11]. This association is rare and corresponds to the case of our patient; similar cases have been reported in the literature.

The pathophysiology of acquired von Willebrand syndrome is characterized by normal or even increased synthesis of vWF, except in cases of hypothyroidism. The low plasma levels observed are mainly due to accelerated clearance of vWF through three principal mechanisms: the presence of neutralizing autoantibodies targeting functional sites of vWF or non-neutralizing antibodies directed against non-functional sites; adsorption of high-molecular-weight multimers (HMWM) of vWF onto tumor cells; and loss of HMWM due to mechanical or enzymatic destruction. These mechanisms are not specific to a single etiology and may coexist [7,8].

In AVWS secondary to MGCS (AVWS-MGUS), the pathophysiology likely involves accelerated immunologic clearance of circulating vWF following its direct binding to the monoclonal antibody. Some studies suggest that monoclonal IgG in patients with MGUS binds in vivo to vWF/factor VIII (FVIII) complexes via a binding site located on the vWF molecule. These complexes are then rapidly cleared by the reticuloendothelial system through an Fc receptor–dependent mechanism [3].

Clinically, the hemorrhagic expression of AVWS is heterogeneous and non-specific, ranging from mild manifestations to severe forms. It varies according to disease severity and subtype [4,9].

Von Willebrand disease is classified into three main types. Type 1, the most common, is characterized by a partial quantitative deficiency of vWF and is usually associated with mild or absent bleeding symptoms. Type 2 corresponds to a qualitative abnormality of vWF and most often leads to moderate symptoms; it represents the majority of acquired forms. Type 3, which is very rare (prevalence of approximately 1 case per 1 million), is defined by a near-complete deficiency of vWF and manifests with spontaneous, sometimes severe and potentially life-threatening hemorrhages, as observed in our reported case [5,9,10].

Biological investigation of AVWS aims to confirm vWF deficiency and to determine its type [9]. Routine tests performed in the presence of hemorrhagic symptoms are necessary but insufficient, including platelet count, which is usually normal; activated partial thromboplastin time, whose prolongation correlates with factor VIII deficiency; bleeding time (BT); and closure time (CT) [9].

According to the recommendations of the French National Authority for Health (HAS), a definitive biological diagnosis requires measurement of total plasma von Willebrand factor antigen, assessment of vWF function as determined by the ability of plasma to induce agglutination of normal platelets in the presence of ristocetin (ristocetin cofactor activity), and measurement of plasma factor VIII levels [6]. The levels observed in our patient were extremely low, consistent with a type 3 deficiency.

Highly specialized investigations exist but are not always required to establish the diagnosis, and some are available only in specialized reference laboratories. However, they allow classification into types and subtypes and characterization of rare forms. These include analysis of vWF multimers, evaluation of vWF binding to factor VIII, platelet binding, and collagen binding [6,9].

Systematic serum protein electrophoresis in elderly patients presenting with AVWS is essential, as recommended by the HAS, in order to search for an underlying monoclonal gammopathy [6].

Etiological diagnosis determines therapeutic management, as treatment of the causal disorder is the only approach that allows sustained regression of AVWS [2,6].

MGUS is not usually treated but requires regular and long-term monitoring due to the risk of progression to a malignant hematologic disorder. When associated with AVWS and severe bleeding, therapeutic management targeting the gammopathy may be discussed within a multidisciplinary team, as in the case of our patient [6].

## CONCLUSION

The diagnosis of acquired von Willebrand syndrome (AVWS) should always be considered, despite its rarity, in elderly patients presenting with spontaneous bleeding of unknown origin.

AVWS may be secondary to monoclonal gammopathy of undetermined significance (MGUS) and result in sometimes severe hemostatic disorders, probably related to the presence of monoclonal autoantibodies directed against von Willebrand factor (vWF).

Early recognition of AVWS, combined with identification of the underlying etiology and initiation of appropriate etiological treatment, allows significant

improvement in both functional and vital prognosis of affected patients.

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