

Successful emicizumab prophylaxis in treatment-refractory acquired von Willebrand syndrome associated with rheumatoid arthritis

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Case Report

Keywords: acquired von Willebrand syndrome, emicizumab, rheumatoid arthritis, von Willebrand factor, factor VIII

Posted Date: October 21st, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-11041695/v1>

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Additional Declarations: No competing interests reported.

Abstract

Acquired von Willebrand syndrome (AVWS) is a rare bleeding disorder characterized by acquired quantitative or qualitative abnormalities of von Willebrand factor (VWF) and may occur in association with autoimmune disease. Management can be challenging when conventional hemostatic and immunomodulatory therapies fail. We report a 63-year-old man with longstanding rheumatoid arthritis (RA) and no personal or family history of abnormal bleeding who developed life-threatening hemorrhage following dental extractions, resulting in airway obstruction requiring tracheostomy and red blood cell transfusion. Evaluation demonstrated an isolated prolonged activated partial thromboplastin time, markedly reduced factor VIII (FVIII) activity, profoundly decreased VWF antigen and activity, and no detectable FVIII inhibitor. The late onset of bleeding, negative genetic testing, poor VWF recovery following high-dose VWF/FVIII concentrate, and underlying autoimmune disease supported a diagnosis of AVWS. Severe VWF deficiency persisted despite treatment with rituximab, methotrexate, and intravenous immunoglobulin (IVIG). Emicizumab was subsequently initiated for prophylactic hemostasis. The patient remained free of spontaneous bleeding despite persistent severe reductions in VWF and FVIII measurements and subsequently underwent upper endoscopy with biopsy and colonoscopy without hemorrhagic complications using adjunctive tranexamic acid. To our knowledge, this represents the first reported case of RA-associated AVWS successfully managed with emicizumab prophylaxis. This case demonstrates sustained clinical hemostasis with emicizumab in treatment-refractory AVWS associated with RA and supports further investigation of FVIII-mimetic therapy as a potential prophylactic strategy when conventional therapies are ineffective.

Introduction

Acquired von Willebrand syndrome (AVWS) is a rare bleeding disorder characterized by quantitative or qualitative abnormalities of von Willebrand factor (VWF) that develop secondary to an underlying condition rather than an inherited VWF defect. In contrast to inherited von Willebrand disease (VWD), AVWS typically presents later in life in patients without a personal or family history of abnormal bleeding. AVWS is most frequently associated with lymphoproliferative, myeloproliferative, and cardiovascular disorders, including patients with left ventricular assist devices, although autoimmune diseases represent an additional recognized cause [1–2].

The pathophysiology of AVWS is heterogeneous and includes antibody-mediated accelerated clearance or functional inhibition of VWF, adsorption of VWF onto cellular surfaces, increased shear-mediated proteolysis, and, less commonly, reduced VWF synthesis [1]. Accordingly, therapeutic responses vary considerably. Management includes treatment of the underlying disorder and control or prevention of bleeding using therapies such as desmopressin, VWF-containing concentrates, antifibrinolytics, intravenous immunoglobulin (IVIG), immunosuppression, and other hemostatic agents [3].

Emicizumab is a bispecific monoclonal antibody that bridges activated factor IX and factor X, thereby mimicking the cofactor function of activated FVIII [4]. Although established as prophylactic therapy for

hemophilia A and increasingly used in acquired hemophilia A, experience with emicizumab in AVWS remains extremely limited [5–6]. We report a patient with severe AVWS associated with RA who remained profoundly VWF deficient despite VWF replacement and multiple immunomodulatory therapies but achieved sustained clinical hemostasis following initiation of emicizumab.

Case Report

A 63-year-old man with longstanding RA was referred to hematology in December 2024 for evaluation of a newly acquired bleeding disorder. He had no previous history of abnormal bleeding and no known family history of bleeding disorders. In June 2024, he developed severe persistent hemorrhage following dental extractions, resulting in upper airway obstruction requiring tracheostomy and a one-month hospitalization. A percutaneous gastrostomy tube placed during the hospitalization was also complicated by oozing, and he developed anemia requiring transfusion of two units of packed red blood cells. Evaluation at the outside hospital demonstrated a prolonged activated partial thromboplastin time (aPTT), normal prothrombin time (PT), FVIII activity of 7%, and a mixing study reportedly demonstrating partial correction.

At initial hematology evaluation six months later, laboratory testing demonstrated a persistently prolonged aPTT of 57.6 seconds with normal PT (10.7 seconds) and international normalized ratio (0.96). FVIII activity remained markedly reduced at 10.4%. Hemoglobin had recovered to 13.9 g/dL and platelet count was normal at $254 \times 10^9/L$. Given the isolated aPTT prolongation, reduced FVIII activity, late onset of bleeding, and underlying autoimmune disease, acquired hemophilia A was initially suspected.

Subsequent evaluation, however, demonstrated no detectable FVIII inhibitor (0 Bethesda units), and repeat mixing studies were consistent with a factor deficiency. VWF testing revealed profound quantitative and functional deficiency, with VWF antigen of 7.3% and ristocetin cofactor activity (RCoF) < 15%. There was no response to ristocetin induced platelet aggregation and vWF multimeric analysis revealed complete absence of all multimers. Lupus anticoagulant and antiphospholipid antibodies were negative. Although the laboratory phenotype initially raised consideration of inherited VWD, the absence of a lifelong bleeding phenotype or family history and negative VWF genetic testing favored an acquired disorder. In the setting of longstanding autoimmune disease, the findings were considered consistent with AVWS associated with RA.

The patient subsequently underwent VWF recovery studies using plasma-derived VWF/FVIII concentrate (Humate-P). Sequential administration of 40 U/kg and 60 U/kg increased FVIII activity to approximately 28% but VWF antigen and activity failed to demonstrate meaningful recovery. The unexpectedly poor recovery of infused VWF provided additional support for an acquired process in the context of his clinical presentation.

Given suspected immune-mediated AVWS, he received rituximab 375 mg/m² weekly for four doses, with the final infusion administered on June 6, 2025. Severe VWF deficiency persisted despite therapy. On

May 30, 2025, FVIII activity was 7.2%, VWF antigen 5.0%, and RCoF < 15%. Repeat testing on July 10 demonstrated FVIII activity of 6.0%, VWF antigen 6.7%, and RCoF < 15%. He also experienced gingival bleeding following brushing his teeth that prompted evaluation in the emergency department, although the bleeding resolved spontaneously.

Because additional dental treatment remained necessary, a periprocedural hemostatic strategy was developed. In August 2025, he received Humate-P 60 U/kg and tranexamic acid 1,300 mg immediately before dental intervention, followed by oral tranexamic acid 1,300 mg every 8 hours for seven days. An additional Humate-P dose was planned for the following day, and dental treatment was successfully completed.

In September 2025, he presented with gastrointestinal bleeding and a hemoglobin of 5.4 g/dL. He was treated with Humate-P 60 U/kg every 12 hours and tranexamic acid (TXA) and received numerous units of packed red blood cells with eventual cessation of bleeding.

Persistent severe VWF deficiency despite VWF replacement and rituximab prompted an additional trial of immunomodulatory therapy. The patient received IVIG 1 g/kg on December 8 and 9, 2025. Repeat testing in January 2026 demonstrated no meaningful laboratory response, with FVIII activity of 6.3%, RCoF < 19%, VWF antigen < 8.5%, and aPTT of 55.8 seconds. His RA was managed concurrently by rheumatology with methotrexate (MTX).

Given persistent severe AVWS despite VWF replacement, rituximab, MTX and IVIG, emicizumab prophylaxis was initiated in February 2026. The initial treatment plan consisted of emicizumab 210 mg subcutaneously weekly, with subsequent transition to a maintenance regimen of approximately 3 mg/kg (210 mg) every two weeks. Following initiation of emicizumab, the patient reported no spontaneous bleeding or clinically significant bruising.

Notably, clinical hemostasis was achieved despite persistence of profound abnormalities in conventional VWF and FVIII measurements. In May 2026, VWF antigen remained 5.1%, RCoF 17.3%, and chromogenic FVIII activity 3.8%. Nevertheless, the patient remained clinically free of bleeding.

In July 2026, while receiving emicizumab prophylaxis, the patient underwent elective esophagogastroduodenoscopy and colonoscopy with adjunctive peri-procedural tranexamic acid. Upper endoscopy demonstrated Los Angeles grade B esophagitis, and gastric biopsies were obtained. Colonoscopy demonstrated nonbleeding hemorrhoids. No immediate or delayed procedural bleeding was reported.

At follow-up in September 2026, the patient remained on emicizumab 210 mg every 14 days and MTX for RA. He denied spontaneous bruising, epistaxis, gingival bleeding, hematemesis, melena, hematochezia, hematuria, or other bleeding manifestations. Serial monitoring of labs revealed VWF antigen < 8.5%, RCoF activity < 19%, and chromogenic FVIII activity 2.9%.

Discussion

AVWS is a heterogeneous acquired bleeding disorder that can closely resemble inherited VWD clinically and biochemically. Laboratory assessment may also be complicated by discordance between VWF antigen and activity, emphasizing the importance of interpreting VWF assays within the broader clinical context [7]. The distinction is particularly important in adults who develop new-onset bleeding without a previous personal or family bleeding history [1, 8]. In our patient, life-threatening hemorrhage after dental extraction in his seventh decade represented the first major bleeding event. The combination of markedly decreased VWF antigen and activity, low FVIII activity, negative FVIII inhibitor testing, negative genetic testing, and poor VWF recovery following VWF/FVIII concentrate supported the diagnosis of AVWS rather than inherited VWD or acquired hemophilia A.

The association between AVWS and autoimmune disease is well recognized but considerably less common than its association with lymphoproliferative, myeloproliferative, and cardiovascular disorders [1, 8]. Proposed mechanisms of autoimmune-associated AVWS include VWF-neutralizing autoantibodies and non-neutralizing antibodies that accelerate VWF clearance. Importantly, measurable VWF inhibitors are detected in only a minority of patients with AVWS; therefore, absence of a demonstrable inhibitor does not exclude an immune-mediated mechanism [1, 8]. The markedly poor recovery of VWF following high-dose VWF/FVIII concentrate in our patient is compatible with accelerated clearance or another acquired mechanism, although the precise mechanism was not established.

AVWS associated with RA appears to be particularly uncommon. Previous reports have described AVWS in patients with RA or overlapping systemic autoimmune disease. Martínez-Murillo et al. described acquired VWF abnormalities in a patient with RA [9], while Hernández-Gilsoul et al. subsequently reported AVWS in the setting of inflammatory arthritis with suspected RA/systemic lupus erythematosus overlap and marked polyclonal hypergammaglobulinemia [10]. These limited reports highlight the rarity of RA-associated AVWS and the heterogeneity of its clinical presentation. In our patient, the absence of an identifiable alternative underlying disorder, together with longstanding RA and poor VWF recovery following replacement therapy, supported a possible autoimmune mechanism.

Management of AVWS requires both control of bleeding and, whenever possible, treatment of the underlying disorder. Hemostatic therapies include desmopressin, VWF/FVIII concentrates, antifibrinolytics, and IVIG, while immunosuppressive treatment may be useful in immune-mediated disease [1, 8]. Responses are often transient because the underlying mechanism responsible for VWF loss remains active [1, 8]. Our patient demonstrated inadequate VWF recovery following high-dose VWF/FVIII concentrate and persistent severe deficiency despite rituximab and IVIG, creating a need for an alternative strategy for long-term bleeding prophylaxis.

Emicizumab offers a mechanistically distinct approach. The bispecific antibody binds activated factor IX and factor X, mimicking the cofactor function of activated FVIII and enhancing thrombin generation [11]. Because VWF normally protects circulating FVIII from degradation, severe VWF deficiency may result in profound secondary FVIII deficiency [1, 8]. Emicizumab can partially bypass this consequence without

replacing VWF itself. It therefore would not be expected to normalize VWF antigen or activity and does not directly restore the VWF-dependent platelet adhesion that contributes to primary hemostasis [11].

The experience with emicizumab in AVWS is only beginning to emerge. In 2026, Vujčić et al. reported emicizumab prophylaxis in a patient with multiple myeloma-associated AVWS, recurrent gastrointestinal angiodysplasia, and life-threatening hemorrhage refractory to multiple therapies [6]. Emicizumab, used as part of a multimodal strategy, was associated with cessation of bleeding and freedom from transfusion despite persistently undetectable VWF activity (6). That report demonstrated the potential for restoration of FVIII-dependent secondary hemostasis to produce clinically meaningful bleeding control even without correction of the underlying VWF abnormality.

Our case extends this emerging experience to severe AVWS occurring in association with autoimmune disease. To our knowledge, this represents the first reported case of RA-associated AVWS successfully managed with emicizumab prophylaxis. The response is notable for the dissociation between conventional laboratory parameters and clinical hemostasis. Despite VWF antigen of 5.1%, VWF activity of 17.3%, and chromogenic FVIII activity of 3.8% in May 2026, the patient remained free of spontaneous bleeding after initiation of emicizumab. Furthermore, he subsequently tolerated upper endoscopy with mucosal biopsy and colonoscopy without hemorrhagic complications.

The procedural outcome should be interpreted cautiously. Tranexamic acid was administered peri-procedurally and likely contributed to mucosal hemostasis; therefore, absence of procedural bleeding cannot be attributed to emicizumab alone. Similarly, this single case cannot establish efficacy or an optimal dosing regimen for emicizumab in AVWS. Emicizumab does not correct the underlying VWF defect, and patients may remain vulnerable to bleeding that depends predominantly on impaired primary hemostasis. Nevertheless, the sustained absence of spontaneous bleeding despite persistent severe biochemical disease following failure of several conventional approaches suggests a clinically meaningful prophylactic effect.

In conclusion, we describe severe, treatment-refractory AVWS associated with RA in a patient who achieved sustained clinical hemostasis following initiation of emicizumab despite persistent profound abnormalities of VWF and FVIII. Together with emerging experience in AVWS of other etiologies, this case suggests that FVIII-mimetic therapy may represent a potential prophylactic strategy for selected patients with severe AVWS when conventional replacement and immunomodulatory therapies are ineffective. Further experience is required to define its efficacy, safety, optimal dosing, and role in peri-procedural management.

Declarations

Ethics approval: Institutional Review Board approval was not required for this single-patient case report in accordance with institutional policy.

Consent for publication: Informed consent was obtained from the patient for publication of this case report.

Competing interests: The authors declare no competing interests.

Funding: No funding was received to assist with the preparation of this manuscript.

Use of AI-assisted language tools: The authors used ChatGPT (OpenAI) for language editing and stylistic improvement of the manuscript text. All scientific content was developed by the authors, who reviewed and approved the final manuscript and take full responsibility for its content.

Author contributions: Evan Botterman contributed to the literature review and drafted the manuscript. Ravi Upadhyay contributed to the clinical management of the patient and critically revised the manuscript. Zachary Israeli and Yash Shah contributed to the literature review and critically revised the manuscript. Alice Cohen contributed to the clinical management of the patient, supervised the preparation of the case report, and critically revised the manuscript. All authors read and approved the final manuscript.

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