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CASE REPORT

Successful Chemical Synovectomy in a Patient with Acquired von Willebrand Syndrome with Chronic Synovitis Due to Recurrent Knee Hemarthrosis: A Case Report

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ABSTRACT

Acquired von Willebrand syndrome (AVWS) is a rare, non-hereditary bleeding disorder related to heterogeneous medical conditions such as hematological malignancies and cardiovascular and autoimmune diseases. We describe the clinical course of a 62-year-old man with polycythemia vera who experienced post-traumatic knee and leg swelling due to hemarthrosis. He was treated at another center with low molecular weight heparin due to misdiagnosed deep vein thrombosis further exacerbating the ongoing bleeding. At our center, he was diagnosed with AVWS with reduced von Willebrand factor (VWF):GPIbR plasma activity and loss of high molecular weight multimers (HMWM). He was treated with compressive bandages with resolution. Five months later, on clinical recurrence of knee and leg swelling, knee ultrasound scan showed the presence of chronic synovitis and a hemorrhagic Baker's cyst with signs of rupture. The treatment consisted of chemical synovectomy with rifampicin and steroids preceded by systemic replacement therapy using plasma-derived factor VIII-VWF concentrate. At the end of the treatment cycle, our patient reported complete resolution of knee pain and restoration of joint range of motion and function. Ultrasound evaluation confirmed complete resolution of knee capsule distension and Baker's cyst. Hemarthrosis is an anecdotal presentation of AVWS and chemical synovectomy was successful in treating this complication. A multidisciplinary approach allowed an effective management of this rare complication.

Keywords: Hemarthrosis; Acquired von Willebrand syndrome; Chemical synovectomy

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Key Summary Points

Acquired von Willebrand syndrome is often associated with myeloproliferative neoplasms, thus leading to an unstable balance between a prothrombotic state and a bleeding tendency.

Clinicians should be aware of the possibility of hemarthrosis in the course of acquired von Willebrand syndrome, even after a diagnosis of cancer-related bleeding disorder.

A multidisciplinary approach is pivotal to tackle rheumatological complications of acquired bleeding disorders.

Chemical synovectomy proved effective in treating blood-induced synovitis and preventing recurrent hemarthrosis in the course of acquired von Willebrand syndrome.

DIGITAL FEATURES

This article is published with digital features, including video files, to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.20199818.

INTRODUCTION

Acquired von Willebrand syndrome (AVWS) is a rare, non-hereditary bleeding disorder associated with heterogeneous underlying conditions such as lymphoproliferative disorders (around 50% of cases, prevalently monoclonal gammopathy of undetermined significance and multiple myeloma), cardiovascular diseases (21%), myeloproliferative neoplasms (15%), and immune disorders (2%) as reported by the first systematic registry by the International Society of Hemostasis and Thrombosis (ISTH) in 2000 [1]. Its precise prevalence and annual incidence are not exactly known due to its rarity, but it typically occurs in adult patients with no family or personal history of bleeding. It presents with mucocutaneous bleeding [2] (bruising, epistaxis, menorrhagia, gastrointestinal bleeding and excessive post-surgical or post-dental extraction blood loss). Compared to congenital hemophilia A and B, which are characterized by recurrent joint bleeding episodes [3] resulting in chronic arthropathy [4] and muscular hematomas, hemarthrosis in the course of AVWS is anecdotal and mainly and post-procedural or post-traumatic [5–7]. The established treatment of chronic synovitis in hemophilia is synovectomy, which can be surgical, chemical, or radioactive [8]. Recurrent hemarthrosis in AVWS is rare and reports of its management are scarce.

Here, we describe the clinical course of a 62-year-old man with polycythemia vera (PV) who developed AVWS and experienced recurrent post-traumatic and spontaneous knee bleeding episodes leading to chronic synovitis. He was successfully treated with coagulation factor VIII (FVIII)-von Willebrand factor (VWF) concentrate replacement therapy and rifampicin-based chemical synovectomy.

METHODS

The present case report has been written according to the CARE guidelines. The Milan Area 2 Ethics Committee has approved the publication of this case report. This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments.

RESULTS

A Caucasian 62-year-old man was referred to the Angelo Bianchi Bonomi Hemophilia and Thrombosis Center of our hospital due to suspected AVWS in August 2020 (Fig. 1).

Six years earlier, he was diagnosed with PV for which he was regularly followed-up at the Hematology Division of our hospital. His first-line treatment consisted of periodical

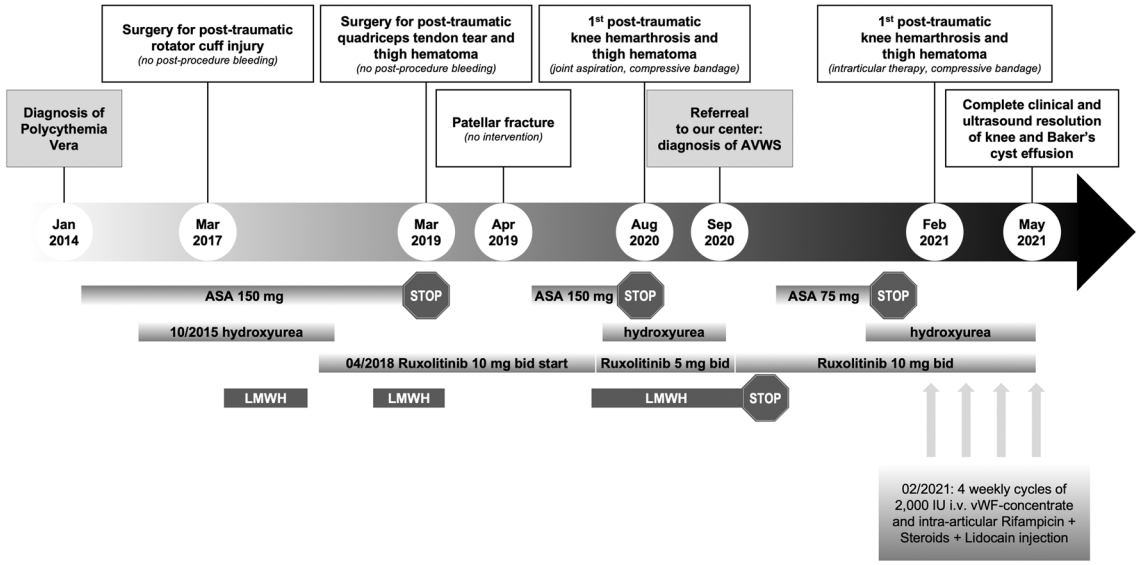

Fig. 1 Timeline of the present case report

venesection, low-dose acetylsalicylic acid (ASA)—initially at a dosage of 100 mg/day, subsequently increased up to 150 mg/day—, and hydroxyurea, which was switched to ruxolitinib after 4 years due to intolerance and systemic symptom persistence. His family medical history was unremarkable.

In 2017, he experienced right shoulder trauma leading to rotator cuff injury, for which he underwent arthroscopic long biceps tenotomy and acromioplasty. Post-operative low molecular weight heparin (LMWH) thromboprophylaxis was administered with no hemorrhagic complications. In 2018, he had a first syncopal episode leading to right knee trauma and muscular hematoma in the right thigh, which was topically treated with compressive zinc oxide paste bandages. Cardiological and neuroradiological investigations were performed with no significant findings, eventually leading to the diagnosis of vasovagal syncope. In March 2019, another accidental fall led to post-traumatic right quadriceps tendon tear presenting with coexistent thigh and leg hematoma, for which he underwent tenorrhaphy. During hospitalization, he experienced anemia (hemoglobin nadir: 8 g/dl) with no hemodynamic instability and no need to receive red blood cell transfusions. Due to the significant drop in hemoglobin levels and expanding muscle hematoma, ASA and ruxolitinib were temporarily withheld, although LMWH thromboprophylaxis was continued. In April 2019, a second syncopal episode provoked right patella fracture managed with conservative treatment.

In August 2020, after a minor trauma to the lower limbs, he presented to a peripheral hospital for first aid with acute severe pain (9 points on visual analogue scale [VAS]), a need for walking aids, and had swelling in the right knee and bruises on the ipsilateral thigh. Based on the clinical suspicion of deep vein thrombosis (DVT), he was treated with a therapeutic dose of LMWH (6000 IU bid) and zinc oxide paste topical bandages. The patient subsequently referred to another orthopedic emergency department due to symptom persistence. There, an arthrocentesis was performed showing hemorrhagic joint effusion, but no further therapeutic interventions were suggested.

When referring to our center following hematologist oncologist advice, he reported persistent pain (8–9 points on VAS) and physical examination showed right knee swelling and functional limitation associated with thigh and leg hematoma.

Complete blood count showed mild microcytic anemia (hemoglobin 12.6 g/dl, mean corpuscular volume 69.2 fl), neutrophilic

leukocytosis (15,910 white blood cells/mm^3; 12,800 neutrophils/mm^3) and mild thrombocytosis (565,000/mm^3); hepatic function, serum creatinine, iron status, prothrombin time (PT ratio 1.01) and activated partial thromboplastin time (aPTT ratio 0.94) were normal. Despite normal antigenic levels of VWF (VWF: Ag 102%, normal values 55–165%) and FVIII activity (FVIII:C 104%; normal values 50–147%), further laboratory investigations were pursued in the hypothesis of AVWS, which was confirmed by reduced VWF activity, measured by a ristocetin-triggered GPIb binding assay (VWF:GPIbR 27%; normal values 50–168%), and loss of HMWM [9]. Even in the absence of a paraprotein at serum protein electrophoresis, circulating anti-VWF antibodies were searched for and resulted negative (Table 1).

The treatment of the acute episode consisted of compressive bandages, temporary discontinuation of ASA and LMWH, and no transfusion support. Desmopressin (DDVAP) was considered as a possible strategy to control acute bleeding but could not be tested at that time due to the patient's uncontrolled elevated arterial blood pressure values. A couple of weeks later, after the resolution of hemarthrosis and muscular hematoma, standard therapy was re-established.

Five months later, our patient experienced recurrence of acute pain and swelling in the previously affected knee. He denied any recent trauma but reported mild physical exercise. Musculoskeletal ultrasound examination of the affected knee was performed, revealing joint capsule distension due to fluid collection and mild synovial hyperplasia in the medial parapatellar recess (see Fig. 2A) and the presence of a 2.7 × 15 cm popliteal cystic lesion extending to the calf (see Fig. 2B). The content of the lesion was an inhomogeneous isoechogenic tissue consistent with organized serohemorrhagic synovial fluid surrounded by hyperplastic synovial membrane, with perilesional tissue edema suggestive of ruptured Baker's cyst (see video 1 in the online/HTML version of the manuscript or follow the digital features link under the abstract).

Magnetic resonance evaluation confirmed synovial thickening with hyperthrophic villous projections of the knee and the presence of a voluminous Baker's cyst (see Video 2 and 3 in the online/HTML version of the manuscript or follow the digital features link under the abstract).

Laboratory tests were performed, showing normal hemoglobin values (13.6 g/dL), persistent neutrophilia (white blood cells 14,980/mm^3, neutrophils 11,960/mm^3) and thrombocytosis (640,000/mm^3), with FVIII:C and vWF:Ag in normal ranges and persistently decreased VWF activity (VWF:GPIbR 30%). In

Table 1 Laboratory tests of the patient

	1st hemarthrosis episode AVWS diagnosis	2nd hemarthrosis episode	After chemical synovectomy
Anti-VWF autoantibodies	Negative	–	–
VWF:Ag (%)	102	105	104
VWF:GPIbR (%)	27	30	64
FVIII (%)	104	110	132
HMWM (%)	Reduced	NA	NA
VWF:CB (U/dl)	79	NA	NA
Platelets (n/mm^3)	796,000	640,000	314,000

Ag antigen, *AVWS* acquired Von Willebrand syndrome, *CB* collagen binding, *FVIII* coagulation factor VIII, *GPIbR* glycoprotein I b receptor, *HMWM* high molecular weight multimers, *NA* not available, *VWF* von Willebrand factor

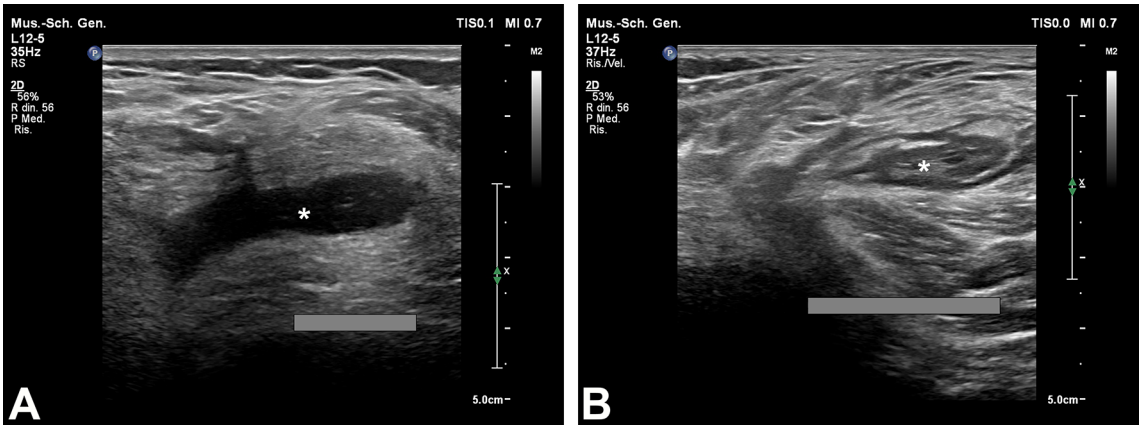

Fig. 2 Medial parapatellar recess, transverse scan (**A**); popliteal fossa, transverse scan (**B**)

order to manage chronic synovitis and to prevent further joint bleeding, we decided to perform chemical synovectomy of the affected knee. The patient underwent four weekly intra-articular injections of rifampicin (2 ml), methylprednisolone (40 mg) and lidocaine (1 ml). The procedure was performed through a lateral suprapatellar approach in order to perform a synovectomy of the whole knee, followed by cryotherapy and rest for at least 2 days following each injection. Considering the low levels of VWF activity, we withheld the anti-platelet medication and a prophylaxis with intravenous plasma-derived VWF concentrate (2000 IU Wilfactin®, Kedrion) was administered prior to each procedure. After the first injection, significant reduction in joint swelling and relief from pain was reported by the patient, and after two cycles, an ultrasound scan documented the resolution of capsule distension and significant reduction of popliteal cyst dimensions. At the end of the full course of chemical synovectomy, the patient reported complete resolution of knee pain, progressive restoration of function and range of motion of the affected joint, and no need for walking aids. The ultrasound scan (see Fig. 3) documented a complete resolution of Baker's cyst and laboratory test showed a hemoglobin level of 13.8 g/dl, platelet count of 314,000/mm^3, white blood cell count of 11,940/mmc (neutrophils 9,150/mm^3), FVIII 132%, vWF:Ag 104% and vWF:GPIbR 64%.

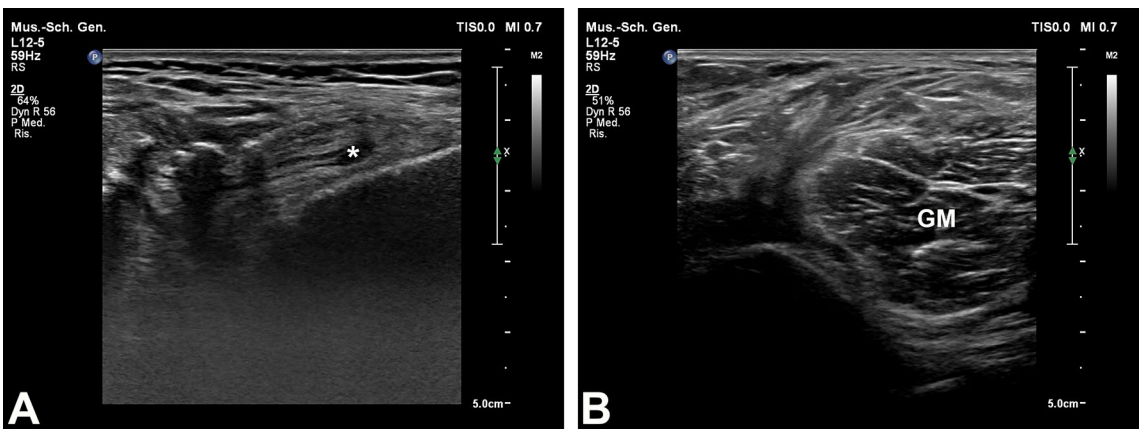

Fig. 3 Medial parapatellar recess, transverse scan (**A**); popliteal fossa, transverse scan (**B**)

DISCUSSION

AVWS is a rare, non-hereditary bleeding disorder, associated with different hematological, cardiovascular, and autoimmune diseases, presenting in patients with no family or personal history of bleeding [1]. Usual presentation consists of mucocutaneous bleeding or excessive post-surgical or post-traumatic hemorrhage. The main laboratory findings are represented by low levels of VWF activity. Normal levels of VWF:Ag or FVIII:C do not exclude this diagnosis. The pathophysiological basis of VWF functional defect is thought to reflect an increased clearance of VWF [10], although few cases report abnormal endothelial and megakaryocyte synthesis [11]. Over the last years, many mechanisms have been proposed, such as circulating anti-VWF autoantibodies in lymphoproliferative [12] and autoimmune disorders [13], selective HMWM adsorption on cell surface in myeloproliferative neoplasms (MPNs) [14, 15], and VWF cleavage induced by high shear stress in cardiovascular diseases [16, 17]. By contrast, acquired hemophilia A is typically characterized by the presence of anti-FVIII antibodies developing in a patient with no history of bleeding events, and clinical manifestations mainly consist of subcutaneous and muscular hematomas, whereas joint bleeding has been rarely reported [18]. On the other hand, inhibitors observed in around one-third of patients with congenital hemophilia A have different kinetic features compared to anti-FVIII antibodies found in acquired hemophilia A. However, in both cases, the interference of these antibodies with FVIII replacement therapy leads to the need of bypassing agents [19]. Indeed, in the case of inherited bleeding disorders such as hemophilia A and B and VWD, when plasma levels of FVIII are markedly reduced, joint bleeding is a typical presentation [20–22]. It has been suggested that joint disease in inherited bleeding disorders draws its origin from a series of subsequent local events, as described by the pathogenetic model of hemophilic arthropathy; indeed a first joint bleeding event leads to synovial inflammation and thickening, thus resulting in a repairing tissue in which angiogenesis, local pro-inflammatory cytokine production, and macrophage-derived metalloproteinase release leading to synovial hyperplasia with an increased risk of recurrent bleeding and subsequent irreversible cartilage and subchondral bone damage [8, 23, 24].

Joint bleeding has been rarely reported in AVWS [25]. Only a few cases of post-procedural [6] or post-traumatic [5–7] joint bleeding in AVWS have been reported in the literature, with only one report describing subsequent chronic synovitis [6], which was managed with arthroscopic synovectomy. In consideration of the anecdotal report of chronic synovitis in this subset of patients, evidence is scarce and a consensus on its management is lacking. Conversely, more consistent literature is available on the local management of chronic synovitis associated with hemophilia A and B, which generally consists of chemical, radioactive, or surgical synovectomy (either via arthroscopic or open surgery) [26].

The rationale behind performing synovectomy in chronic synovitis consists of breaking the described vicious cycle of synovial inflammation due to recurrent hemarthrosis and subsequent re-bleeding, thus ameliorating symptoms and function of the affected joints [8, 26]. Chemical synovectomy bases its efficacy on the sclerosing activity of different drugs, such as oxytetracycline and rifampicin [27, 28]. Over the last three decades, several single-center observational studies reported a good safety profile and efficacy of rifampicin in hemophilia in terms of both clinical [28, 29] and radiological improvement [30], especially in ankles and elbows. The main advantages of this procedure are represented by the minimally invasive administration, the low costs, and possibility to start rehabilitation shortly after the end of the repeated intra-articular injections. On the other hand, multiple injections are needed, particularly in larger joints such as the knee [29, 31]. Radiosynoviorthesis, which is performed through the intra-articular injection of radionuclide such as Yttrium-90, proved to be effective as well, despite the high costs and problems regarding radioisotope availability and wasting management [32–35]. It is generally performed in an outpatient setting and

generally requires only one administration, which can be repeated after 3–6 months, if needed [26].

To date, only one non-randomized prospective study involving few patients aged nine or older compared chemical and radioactive synovectomy demonstrating comparable efficacy of both procedures [31]. Joint embolization or arthroscopic synovectomy can be performed when huge synovial hyperplasia is present [8], differently from our case in which synovial hyperplasia was limited. Similar observations for either non-surgical or surgical synovectomy have been done in inherited VWD, although data available from the literature are more limited [21]. In our case, we chose chemical synovectomy over radiosynoviorthesis because of its easier handling and lower costs with no radioactive waste-disposal concerns.

In our case, it is likely that the significant worsening of knee bleeding in the first place was related to inappropriate LMWH prophylaxis prescribed in a MPN patient with prothrombotic diathesis. A recent systematic review, focusing on data collected from 16 retrospective studies in PV patients between 2005 and 2018, showed a median incidence of any bleeding event and major bleedings of 15.3 and 6.5% respectively, over a median follow-up period of 4.5 years [36]. On the other hand, ASA discontinuation for surgery may have shifted the hemostatic balance towards a prothrombotic state; therefore, a conservative treatment was chosen. Our observations are supported by a large retrospective study [37] in a cohort of 311 patients with PV undergoing surgery that showed a high prevalence of both thrombotic events and major hemorrhage of 7.7 and 7.3% independent of thromboprophylaxis or antiplatelet drug discontinuation. One could argue that our patient had laboratory features congruent with AVWS even if he had a near normal platelet count. Cases with near-normal platelet count have been described as well [38]. In a retrospective analysis by Mital et al., up to one-third of patients with MPN with a median platelet count $< 700{,}000$ had AVWD [39]. This could be explained by the selective loss of HMWM. Antiplatelet therapy was restarted as soon as the bleeding episode had resolved, after careful evaluation of the bleeding risk, as per international recommendations [40] and the patient has not experienced any other major bleeding events so far.

Due to the difficult management of patients with AVWS in MPN, an accurate evaluation of the prothrombotic and bleeding risk should be performed in each patient. We suggest that a multi-disciplinary consultation is warranted in these complex cases.

CONCLUSIONS

Point-of-care musculoskeletal ultrasound proved a very useful tool in detecting rare complications of AVWS such as hemarthrosis and hemorrhagic Baker's cyst. The latter is often misdiagnosed for DVT in patients with a condition that increases prothrombotic risk, such as MPN. However, MPN may be associated with the risk of developing an acquired bleeding disorder as well, thus making the identification and management of bleeding events in these patients more challenging.

In conclusion, we report the successful management by chemical synovectomy of recurrent hemarthrosis as a rare complication of AVWS in a patient with PV.

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Disclosures. Roberta Gualtierotti, Claudio De Magistris, Eugenia Biguzzi, Jacopo Acquati Lozej, Alessandra Iurlo, Luigi Piero Solimeno, and Flora Peyvandi declare that they have no conflicts of interest.

Compliance with Ethics Guidelines. The patient provided consent for the publication of the present manuscript and the Milan Area 2 Ethics Committee provided approval for publication.

Data Availability. Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study.

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