Case report

Acquired von Willebrand syndrome associated with plasma cell myeloma – a rare histopathological bone marrow image

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Acquired von Willebrand syndrome (AVWS) is a rare bleeding disorder that is associated with a variety of underlying diseases. We report a case of AVWS associated with plasma cell myeloma. The patient was a 57-year-old male with recurrent bleeding symptoms for a few months. Physical examination was normal. Laboratory studies revealed isolated prolongation of the activated partial thromboplastin time. His factor VIII activity, von Willebrand factor (VWF) Ag, and VWF activity were low. Bone marrow aspirate showed diffuse infiltration of atypical plasma cells and erythroid line hyperplasia.

Key words: acquired von Willebrand syndrome, plasma cell myeloma.

Introduction

Acquired von Willebrand syndrome (AVWS) is a rare bleeding disorder with an estimated prevalence ranging from 0.04 to 0.13% in the general population [1]. The profile of clinical symptoms and laboratory findings is similar to that of congenital von Willebrand disease (VWD). Characteristic features of AVWS include lack of previous clinical bleeding abnormalities, late-onset, and negative family history of bleeding. It is characterised by a prolonged bleeding time (BT) and variably low plasma levels of von Willebrand factor (VWF) and factor VIII (FVIII). Usually this syndrome is associated with lymphoproliferative, myeloproliferative, and cardiovascular diseases or autoimmune disorders. Lymphoproliferative and myeloproliferative disorders appear to be most frequently associated with AVWS as per data in both the literature and the registry, accounting for 48-63% of cases [2]. Acquired von Willebrand syndrome appears to be more frequent in men than in women of advanced age [3]. The severity of bleeding tendency varies from mild to life-threatening.

Case presentation

A 57-year-old male with chronic kidney disease stage 3a presented for the first time to the Institute of Haematology and Transfusion Medicine in Warsaw in 2018 due to repeated episodes of nosebleeds. He had a previous total thyroidectomy because of goitre in 2012, which was complicated by immediate bleeding. The follow-up from the time of strumectomy to the time of the first report to the Institute was unknown. To exclude systemic amyloidosis, fat tissue biopsy was examined by polarised light microscopy after Congo red staining. Amyloid deposits were not

detected. Family history was negative for bleeding disorders.

A full blood count, coagulation screening on admission, and further laboratory analyses are shown in Table I.

The patient's urine contained 270.54 mg of protein in a 24-hour specimen with a creatinine clearance of 2.19 mg/dl. The von Willebrand factor ristocetin cofactor (VWF:RCo) was 1.58%, VWF:Ag 12.81%, and factor VIII 12.81%. Immunofixation electrophoresis of the serum showed a kappa chain of 25.0 mg/l, and lambda chain 1770.99 mg/l. The serum kappa/lambda light chain ratio was 0.01 (reference range 0.26-1.65). Urine electrophoresis showed free light chains. Echocardiography was normal, and no hepatosplenomegaly was detected.

The trephine biopsy demonstrated markedly hypercellular bone marrow (Fig. 1A). The erythroid (CD71 positive) to granulocytic (MPO and CD33 positive) line was 1 to 1-1.5 with a visible population of erythroblasts and megaloid forms (Fig. 1). Single CD34 and CD117 blast cells were recognised and did not exceed 3% of all bone marrow cells. Moreover, the interstitial infiltrates of atypical plasma cells were detected and comprised 15%; in the immunohistochemical study its immunoprofile was positive for CD138, CD56, and lambda, and negative for kappa, CD20, and CD19 (Fig. 2). Flow cytometric immunophenotyping of bone marrow aspirate specimen showed a population of CD138 cell with aberrant phenotypes concordant with trephine biopsy examination. The patient had met the criteria for the diagnosis of plasma cell myeloma according to the International Myeloma Working Group (clonal bone marrow plasma cell percentage ≥ 10% and myeloma-defining events: end-organ damage including renal insufficiency, serum an uninvolved-to-involved serum free light chain ratio 0.01) [4]. Therefore, taking into consideration all the above results, the final diagnosis of AVWS associated with plasma cell myeloma was made. The patient decided to continue treatment at a hospital nearer to their place of residence, and the follow-up in our Institute was discontinued.

Discussion

Acquired von Willebrand disease is a rare haemorrhagic disorder with a profile of clinical symptoms and laboratory findings similar to that of congenital von Willebrand disease (VWD). Unlike VWD, the acquired one usually occurs in individuals with no family history of bleeding. Six categories of underlying disorders have been reported to occur frequently in patients with AVWS: lymphoproliferative and myeloproliferative disorders; solid tumours; immunological and cardiovascular disorders; and miscellaneous conditions [2, 5]. The most frequent clonal disorder associated with AVWS is monoclonal gammopathy of undetermined significance (MGUS), either alone or in association with other plasma cell proliferative disorders, such as multiple myeloma and Waldenström macroglobulinaemia [3, 6, 7]. AVWS associated with multiple myeloma is very rare. According to data from the International Registry, 16 out of 186 (9%) AVWS patients were diagnosed with multiple myeloma. Additionally, in the literature there are approximately 30 reported cases of these two disorders in combination [8, 9, 10, 11, 12, 13, 14].

The pathophysiology of AVWS is highly heterogeneous and not fully understood. Various mechanisms of the acquisition have been postulated depending on the underlying process. Amongst the main and

Table I. A full blood count, coagulation screening on admission, and further laboratory analyses in the presented case

Test	Result	Reference range
White blood cell count	11.78 G/l	3.50-10.00 G/l
Red blood cell count	5.47 T/l	4.50-5.70 T/l
Haemoglobin	10.9 g/dl	12.0-16.8 g/dl
Platelet count	483 G/l	125-400 G/l
Active partial thromboplastin time	53.9 seconds	23.1-36.3 seconds
Prothrombin time-international normalised ratio	1.1 1	0.9-1.2
Blood urea nitrogen	72 mg/dl	10-50 mg/dl
Creatinine	2.19 mg/dl	0.63-1.03 mg/dl
Total protein	62 g/l	64.0-83.0 g/l
Iron	10 μg/dl	59-158 μg/dl
C-reactive protein	7.9 mg/l	< 5 mg/l

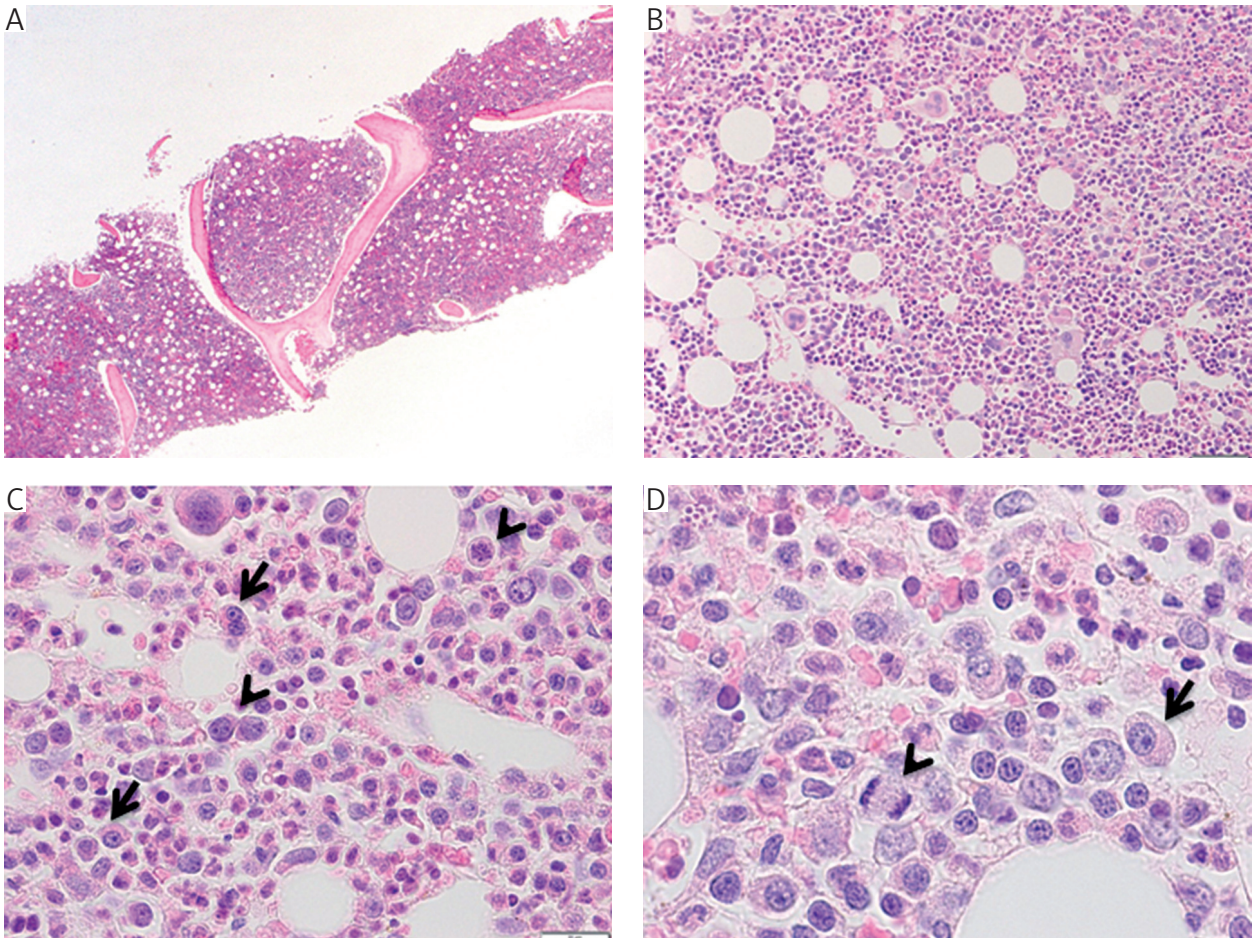

Fig. 1. Trephine biopsy from patient with plasma cell myeloma accompanied with acquired von Willebrand syndrome: A) hypercellular bone marrow (HE, 10×); B) abundant erythroid line (HE, 20×); C, D) numerous erythroblasts and megaloid forms (arrowhead) with visible mitotic activity (arrowhead), and atypical plasma cells (arrow; C – HE, 60×; D – HE, 100×)

well-characterised mechanisms described in AVWS are: the development of a specific inhibitor active against FVIII complex; immunoadsorption of VWF onto a malignant clone of cells; formation of immune complexes between VWF and immunoglobulins; and increased proteolytic degradation of VWF [15, 16]. Other pathogenetic mechanisms include a decrease in VWF protein synthesis in the absence of adequate levels of thyroxine, a decrease in VWF antigen levels by the hyaluronic acid present in Wilm's tumour, accelerated proteolysis of large multimers in association with ciprofloxacin administration, and increased turnover of plasma large VWF multimers in patients with high platelet counts [17]. In patients with lymphoproliferative disorders, AVWS is mainly caused by the development of autoantibodies directed against VWF. Autoantibodies can lead to increased clearance of VWF via the formation of immune complexes or decreased VWF function by interference with functional domains related to collagen or platelet glycoprotein binding. These may bind to the functional epitopes of VWF and neutralise its activity or these antibodies may form immune complexes with VWF, accelerating its clearance from circulation [18]. A functional defect of plasma VWF is induced by binding of these specific inhibitors to functional epitopes of VWF. Secondly, non-neutralising autoantibodies binding to non-functional domains of VWF can accelerate the elimination of the large VWF multimers from the circulation by the formation of immune complexes [8, 19].

In multiple myeloma, proposed possible pathophysiologic mechanisms of AVWS include the inhibiting role of paraprotein, the monoclonal protein produced by the plasma cell clone [1, 20, 21, 22]. Cases of AVWS due to antibodies with inhibitory effects on VWF function have been reported, including abnormal platelet adhesion due to paraprotein binding to VWF A1 domain, which is a glycoprotein 1b binding domain (GP Ib) [21, 23]. Furthermore, Shiganawa *et al.* showed that paraprotein inhibited ristocetin-induced platelet aggregation by direct interference with the 39/34 kD fragment of VWF containing the A1 domain [25]. Impaired platelet aggregation has been associated with non-specific coating of platelet receptors by paraprotein. Paraprotein can

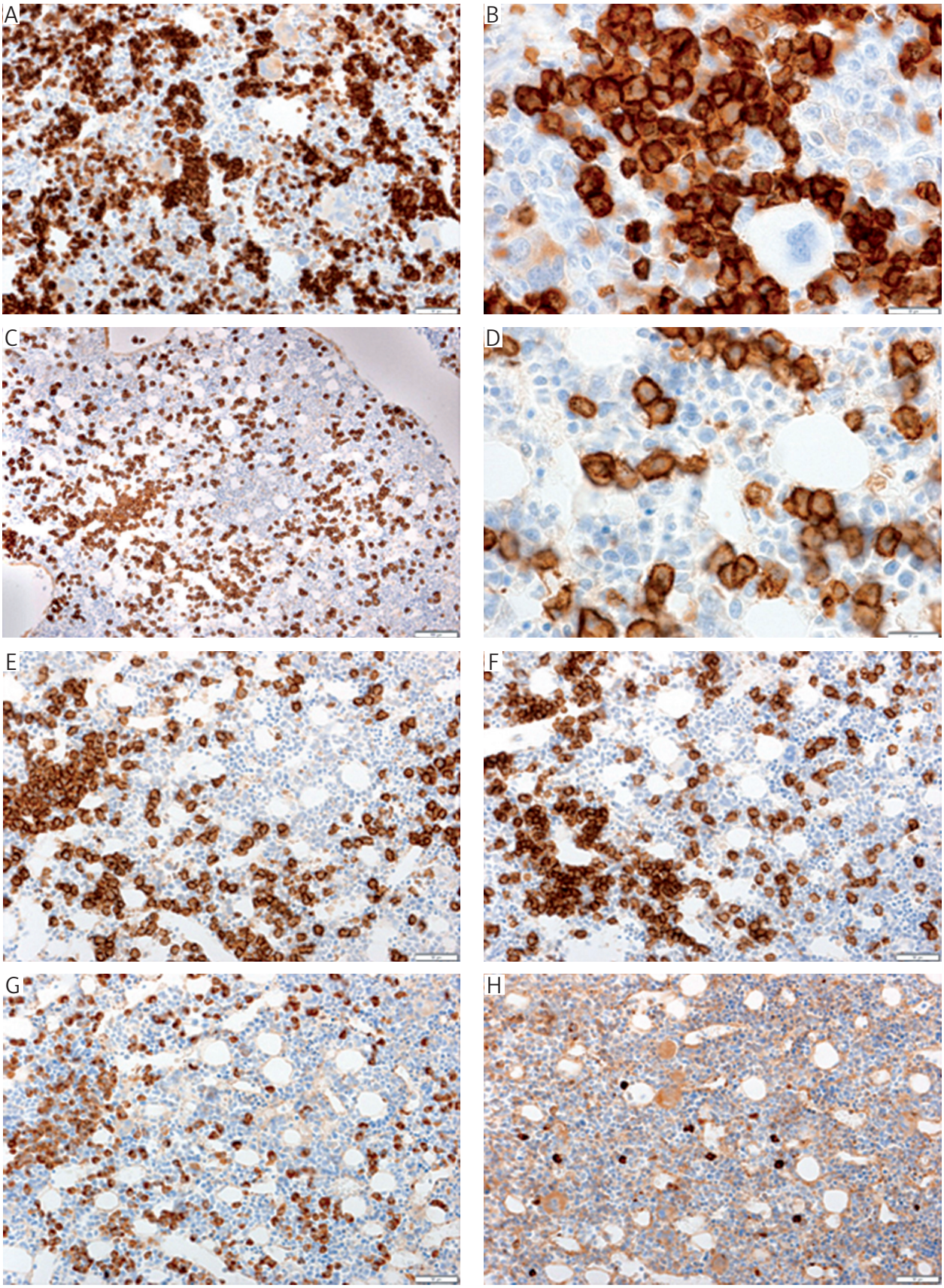

Fig. 2. Trephine biopsy from patient with plasma cell myeloma accompanied with acquired von Willebrand syndrome – immunohistochemical assessment: A, B) abundant erythroid line (A – CD71, 20×; B – CD71, 60×); C) plasma cell myeloma (CD138, 10×); D) plasma cell myeloma in "hotspot" (CD138, 60×); E–H) immunophenotype of plasma cell myeloma (E – CD138, 20×; F – CD56, 20×; G – lambda, 20×; H – kappa, 20×)

also suppress platelet function by specific binding to the VWF Gp 1b binding domain, thereby inhibiting binding of VWF to platelets stimulated by ristocetin, and by binding to platelet IIb/IIIa receptors [24, 35].

In our patient, no inhibitory antibodies against VWF or factor VIII were detected. Such a negative test result does not rule out the diagnosis of AVWS. The detection rate of inhibitors in AVWS is low. Inhibitory activity against FVIII or VWF was confirmed by mixing tests in only 25% of patients with AVWS associated with a lymphoproliferative disorder. However, the autoantibodies may still be present in the circulation despite a negative test result [3, 8, 19].

Diagnosis of AVWS is usually based on the laboratory parameters typical for VWD, except for the absence of a family history of bleeding. BT, VWF ristocetin cofactor activity (VWF:RCo), or collagen binding assay (VWF:CB) in plasma compared with VWF:Ag, ristocetin-induced platelet agglutination, a multimeric analysis in plasma and platelets, and VWF pro-peptide (formerly known as VWF antigen II) have all been used to identify patients with AVWS [2]. Testing for anti-VWF antibodies should always be performed because the presence of these inhibitors is clinically significant [24, 25, 26].

Histologically, the bone marrow in AVWS is hypercellular with increased normoblastic erythropoiesis. The erythroblasts are increased in size but have nuclear and cytoplasmic characteristics similar to those of normoblasts. The number of erythroid islands is increased and the central macrophage is large and prominent, often staining a dirty green colour with a Giemsa stain because of the presence of increased hemosiderin [27].

Recognition of AVWS is challenging, and because of its rarity it is sometimes not taken into account in patients with bleeding disorders. In some cases described in the literature the diagnosis of AVWS was made secondarily to multiple myeloma. Suspicion of AVWS was raised due to prolonged bleeding after surgical procedure or trephine biopsy of the bone marrow [8, 13, 14]. Sometimes an increasing tendency to bleed is the first sign of haematological disorder, which leads to the discovery of multiple myeloma, as in the presented case [11, 12].

In the largest described series and cohorts of patients with AVWS associated with plasma cell myeloma, the authors emphasise that the diagnosis can be difficult but remains crucial because of the risk of severe bleeding during invasive procedures [6, 7]. There are three main treatment goals in AVWS: to control current bleeding episodes; to prevent bleeding when an invasive procedure is necessary; and, when possible, to control the underlying disease. In several disorders associated with AVWS, surgery, chemotherapy, radiotherapy, or discontinuation of the responsible drugs can sometimes control the underlying disease, with the resolution of the bleeding diathesis and normalisation of the laboratory parameters [2]. Because long-term remission of AVWS associated with plasma cell myeloma with bortezomib and dexamethasone therapy or lenalidomide treatment are observed always the possibility of coexistence with lymphoproliferative malignancy should be eliminated [12, 28, 29, 30, 31, 32].

One of the treatment options for control of acute bleeds or prevention of high-risk bleedings is desmopressin infusion, with a relatively good success rate (44%) in lymphoproliferative disorders [10]. According to Takahashi *et al*., a single intravenous infusion of desmopressin is followed by a normalisation of the prolonged bleeding time and marked increase in plasma VWF:Ag and VWF:RCo [33]. To obtain long-term remission of AVWS symptoms, treatment of the underlying disease is necessary. Significant bleeding complications can be a recommendation for treating a multiple myeloma, even when there is no treatment indication for the haematological disease otherwise. Some studies have shown that reduction of bleeding symptoms is not always connected with change in monoclonal IgG or VWF:Ag measurements. Moreover, treatment of the haematological disorder does not always result in improvement of AVWS manifestation [11, 34].

Conclusions

Acquired von Willebrand's syndrome is a clinical condition characterised by mucocutaneous bleeding in individuals who often have underlying conditions such as malignancies, lymphoproliferative processes, autoimmune disorders, or monoclonal paraproteinaemia. Unfortunately, despite evident clinical manifestation, AVWS is frequently overlooked. It can be asymptomatic in mild conditions for decades. AVWS should be considered in cases of abnormal bleeding and prolonged PTT. Early diagnosis and implementation of appropriate therapy prevent severe haemorrhagic complications. Aside from control and prevention of haemorrhage, management of AVWS should also focus on the treatment of the primary underlying condition because achieving its remission is frequently associated with the resolution of the bleeding disorder. In the histopathological examination of bone marrow with suspicious of AVWS the secondary malignancy, especially multiple myeloma, and lymphoproliferative disease should be excluded.

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