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CHAPTER 13

SUCCESSFUL TREATMENT WITH RECOMBINANT FACTOR VIIA OF THERAPY-RESISTANT SEVERE BLEEDING IN A PATIENT WITH ACQUIRED VON WILLEBRAND DISEASE

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Summary

We describe an elderly man who presented with life-threatening hematuria and gastrointestinal bleeding caused by acquired von Willebrand disease associated with monoclonal gammopathy of undetermined significance (MGUS). Standard therapy with desmopressin, von Willebrand factor-containing factor VIII concentrate, tranexamic acid and immunoglobulin failed to achieve adequate hemostasis. However, treatment with recombinant activated factor VII (rFVIIa) arrested the bleeding completely. Since acquired von Willebrand disease can lead to life-threatening hemorrhage, clinicians should consider rFVIIa as an effective treatment option if standard therapy fails.
Recombinant factor VIIa in a patient with acquired von Willebrand disease

Introduction

Acquired Von Willebrand disease (AvWD) is a relatively rare bleeding disorder that usually occurs secondary to an autoimmune disorder or neoplastic disease. Since AvWD was first described as a case report in a patient with systemic lupus erythematosus in 1968, more than 120 cases have been described and reviewed in the literature. Like congenital von Willebrand disease, AvWD is characterised by a defective primary hemostasis, with bleeding as the presenting symptom. Laboratory studies usually show a normal prothrombin time and a prolonged activated partial thromboplastin time, reduction of ristocetin cofactor activity (vWF:RCoF), von Willebrand factor antigen levels (vWF:Ag), factor VIII clotting activity, and a prolonged bleeding time. Treatment is generally aimed at raising von Willebrand factor levels (e.g. by desmopressin or von Willebrand factor concentrates) or eradication of anti-von Willebrand factor antibodies by immunomodulating agents such as prednisone or immunoglobulin. We describe a patient with acquired von Willebrand disease associated with MGUS with severe therapy-resistant hemorrhage who was successfully treated with recombinant factor VIIa.

Case Report

A 73-year-old man was admitted with recurrent macroscopic hematuria without an apparent cause. The patient had a history of benign prostatic hyperplasia, hypertension, angina pectoris and chronic obstructive pulmonary disease. Since one year, he had experienced subcutaneous hematoma and episodes of spontaneous hematuria. Cystoscopy did not reveal any abnormality but was complicated by a sustained worsening of the hematuria. Also, the patient had recently experienced an episode of rectal blood loss due to a bleeding colon diverticulum. He did not use any medication known to affect the coagulation system. Neither the patient nor his family was known with a history of bleeding diathesis.

Laboratory examination revealed anaemia (hemoglobin 5.8 mmol/L) despite multiple red cell transfusions and a normal white blood cell count and platelet count. Coagulation tests showed a normal prothrombin time but a severely prolonged activated partial thromboplastin time (aPTT: 59 sec; normal value <28 sec). The prolongation of the aPTT appeared to be due to low levels of factor VIII:C (3%; normal value >50%). Further examination showed the absence of anti-factor VIII antibodies but undetectable levels of von Willebrand factor (von Willebrand ristocetin cofactor activity <10% and von Willebrand antigen <1%). Von Willebrand factor propeptide was normal (115%) indicating normal synthesis and release of von Willebrand factor. Based upon these results a diagnosis of acquired von Willebrand disease was made, although circulating anti-von
Willebrand factor antibodies could not be directly assessed, which is not uncommon in patients with AvWD. Further testing revealed the presence of an IgG kappa paraprotein (7.2 g/L), but otherwise normal levels of immunoglobulin. A bone marrow aspirate showed 0.9% plasma cells, and an X-ray series did not show any osteolytic lesions. Hence, the diagnosis monoclonal gammapathy of undetermined significance (MGUS) was made, which indeed is known to be associated with acquired von Willebrand disease.\textsuperscript{1,8,10}

Despite therapy during ten weeks that included 82 transfusions with erythrocytes and 23 units of fresh frozen plasma, multiple infusions with desmopressin and von Willebrand factor-containing FVIII concentrates and tranexamic acid, adequate hemostasis was not achieved. Also, prednisone (up to 60 mg/day) and human gammaglobulin were administered (25 g per day) without effect. Instead, the bleeding worsened and the patient was transferred to the Academic Medical Centre for further treatment. At that time, the patient was hemodynamically instable with a blood pressure of 80/40 mm Hg. He was treated with high dose von Willebrand factor-containing factor VIII concentrate (Humate-P, Centeon, Germany), but this was again not effective in controlling the bleeding. At 15 and 90 minutes after 3000 U of Humate-P, vWF RiCoF was 32% and <5% respectively, indicating very rapid elimination of the von Willebrand concentrate. Because standard therapy failed to arrest the bleeding, administration of recombinant activated factor VII (rFVIIa, NovoSeven, NovoNordisk, Denmark) was started at a bolus dose of 90 μg/kg, followed by a continuous infusion of 17.5 μg/kg/hour for 6 days. Hereupon, the bleeding almost immediately stopped and treatment was continued for 6 days. One week after cessation of rFVIIa therapy, the patient produced large volumes of bloody stools. Endoscopy of the colon revealed diverticulosis and three large superficial ulcers in the recto-sigmoid without active bleeding. RFVIIa treatment was again instituted with a bolus dose of 90 μg/kg, followed by a continuous infusion of 17.5 μg/kg/hour in combination with tranexamic acid at 4 g per day. Hereupon, the bleeding stopped, the hematochezia disappeared and the rFVIIa treatment could be terminated after 4 days. Three weeks hereafter, the hematuria recurred and was again immediately effectively arrested by administration of one single bolus dose of rFVIIa of 6 mg. Finally at 7 weeks after admittance, the patient was discharged in a reasonable state and bleeding has not recurred ever since.

Discussion

Acquired von Willebrand disease is a relatively rare bleeding disorder, that has been associated with the presence of several clinical conditions and disorders.\textsuperscript{2} Different treatment regimens of patients with AvWD have been reported, but the variety of
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underlying disorders may explain the changing successes reported so far. Recently, a clinical cross-over trial compared the effects of intravenous immunoglobulin in the prevention or treatment of bleeding episodes in patients with MGUS-related AvWD. In this trial, immunoglobulin was most effective.\textsuperscript{11} Other treatment options have been reported for AvWD disease such as desmopressin,\textsuperscript{12} plasma exchange,\textsuperscript{13} steroids\textsuperscript{14-16} and immunosuppressive drugs,\textsuperscript{17,18} all with varying success. Since our patient did not respond to any of the treatment strategies suggested in the literature, we instituted an alternative hemostatic intervention by administering rFVIIa. RFVIIa has been successfully used in the treatment of patients with antibodies to factor VIII and IX (hemophilia with antibody formation to exogenic coagulation-factor concentrates or acquired hemophilia). Also, a limited number of patients with a variety of defects in the primary hemostasis have been successfully treated with rFVIIa.\textsuperscript{19,22} In vitro studies have shown that rFVIIa can activate coagulation at platelet surfaces, which possibly leads to formation of a stable fibrin network even in the absence of an optimal initial platelet plug. This may explain the efficacy of recombinant factor VIIa treatment in patients with defects in primary hemostasis.\textsuperscript{23} The present case describes the use of rFVIIa in a patient with a defect in primary hemostasis who was challenged by life threatening bleeding due to AvWD. The patient was successfully treated without the development of any side effects such as thromboembolic events. We conclude that if standard therapy fails to control bleeding in a patient with AvWD, clinicians should consider rFVIIa as an effective treatment option.

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References


