Acquired von Willebrand disease associated with free lambda light chain monoclonal gammopathy, normal bleeding time and response to prednisone

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Summary: We report a case of acquired von Willebrand's syndrome with severe gastrointestinal bleeding and associated free monoclonal lambda light chains. The patient had a rapid sustained clinical and laboratory response to the administration of prednisone. Of note in this patient was the occurrence of angiodysplasia which has previously been reported in association with acquired von Willebrand's syndrome. No inhibitors of VWF:Ag, VWF:RCof, or factor VIII:C were detected by mixing studies and the bleeding time was normal. Very few high molecular weight von Willebrand multimers were present prior to prednisone; however, the pattern reverted to a normal distribution following treatment.

In appropriate patients with acquired von Willebrand's syndrome and monoclonal para-proteins, a trial of prednisone may be indicated.

Introduction

Acquired von Willebrand syndrome (VWS) is an uncommon disorder and has been reported in approximately 50 cases to date.¹ The syndrome presents as a spontaneously acquired bleeding disorder, usually associated with severe gastrointestinal or mucosal bleeding, and mimics hereditary von Willebrand's disease. It is distinguished from the hereditary variety by its clear-cut onset later in life, in patients lacking a family history of bleeding diathesis, who have withstood previous haemostatic challenges without excessive bleeding.

In many cases acquired VWS is associated with an abnormal monoclonal paraprotein, usually IgG kappa, occasionally IgG lambda and rarely IgA or IgM.^{2–5} It is also associated with a number of disorders characterized by an acquired immune defect, such as lymphoma, chronic lymphocytic leukaemia, hairy cell leukaemia, polycythemia rubra vera, Waldenstrom's macroglobulinaemia, and systemic lupus erythematosus (SLE).

VWS is also associated with disease in which an immune defect is not so obvious including patients with Wilms' tumour, adenocarcinoma, squamous cell carcinoma, hypersensitivity reactions,

hepatoma, hydatid disease of the spleen and occasionally in patients without an identifiable underlying disorder.^{6–10} VWS has also been implicated in the secondary bleeding disorders associated with myeloproliferative diseases.^{11,12}

We report here a case of acquired von Willebrand's syndrome with a normal bleeding time, arising in association with free lambda light chain disease, which responded to treatment with steroids. Unlike many previous cases,¹³ no inhibitor of von Willebrand factor: ristocetin cofactor (VWF:RCof) activity was detected when mixing studies were performed. At initial examination the profile of VWF multimers showed an absence of the high molecular weight multimers necessary for normal haemostasis. After treatment with prednisone the pattern reverted to a normal distribution.

Case report

A 62 year old female of Italian descent presented in December 1987 complaining of lethargy. Investigation showed a microcytic hypochromic anaemia with haemoglobin of 8 g/dl. In February 1988 she was admitted with a history of upper gastrointestinal bleeding when her haemoglobin was 5.7 g/dl. Endoscopy of the upper gastrointestinal tract revealed telangiectasia throughout. She had no

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previous history of bleeding problems and had delivered three children without excess bleeding.

Over the next four months the patient required frequent admissions to hospital for gastrointestinal bleeding and required multiple red cell transfusions. Laser photo-coagulation of the telangiectasia was performed with some success. In March 1988 a prothrombin time (PT) and partial thromboplastin time (PTT) were normal. In May 1988 a repeat of the coagulation profile showed that the PT remained normal while the PTT utilizing rabbit brain phospholipid and micronised silica (General Diagnostics, Morn's Plains, NJ) was now 38 seconds with a control of 28 seconds (normal range 23 to 34 seconds). In June 1988, a reassessment was performed. At this time whilst the PT was normal the PTT was now 46 seconds. All other one-stage tests of coagulation were normal. The fibrinogen was 2.7 g/l. The bleeding time with a Simplate bleeding time device was 4 minutes. The assays of the coagulant activity for factor IX, XI, XII were within the reference range but the assay of factor VIII was abnormal. The factor VIII coagulant activity (VIII:C) was 0.10 U/ml (reference range 0.7–1.5 U/ml); von Willebrand factor antigen (VWF:Ag) undetectable (ref. 0.6–1.2 U/ml); and VWF:RCoF <0.1 U/ml (ref. 0.6–1.2 U/ml). Mixing studies detected no circulating inhibitors of VWF:Ag, VWF:RCoF or VIII:C.

SDS agarose gel electrophoresis of von Willebrand's factor was performed, multimers were identified by exposing gels to ¹²⁵I-labelled anti-VWF antibody. Autoradiography revealed absence of high and intermediate molecular weight multimers.

Further investigation revealed the presence of circulating free lambda light chains. Quantitative immunoglobulins showed IgG of 5.8 g/dl (ref 8–18 g/dl); IgA 0.1 g/dl (ref 0.9–4.5 g/dl); IgM <0.1 (ref 0.6–2.8 g/dl). Large amounts of free lambda light chains were also detected in the urine. Renal function was normal and a bone marrow aspiration was also normal. The low immunoglobulin levels were felt to be consistent with a possible underlying myeloma.

The patient was treated with cryoprecipitate and given prednisone 60 mg once daily. Repeat of the coagulation profile 3 weeks later, showed factor VIII:C 0.75 U/ml; a VWF:Ag of 0.95 U/ml and VWF:RCoF of 0.38–0.76 U/ml.

Repeat immunoelectrophoresis one month later showed only trace amounts of free lambda. Quantitative immunoglobulins were unchanged. Her steroids were tapered to prednisone 5 mg on alternate days. After 3 months of therapy a crush fracture of T7 vertebrae developed, bone marrow and immunoelectrophoresis were unchanged. Osteopenia was noted and felt to be secondary to her underlying disease.

Discussion

The mechanisms resulting in acquired von Willebrand's syndrome are by no means clear. Production of von Willebrand's factor appears normal based on studies demonstrating that treatment with 1-desamino 8-D arginine vasopressin (DDAVP) may correct the VWF deficiency and normalize multimer formation.^{3,7,8} This newly formed VWF is rapidly cleared from the circulation.

In many cases circulating antibody or abnormal lymphocytes appear to bind VWF.^{2,14,15} The binding of antibody probably occurs on an inactive portion of factor VIII (removed from factor VIII:C).¹³ Subsequently the majority of published reports fail to show inhibition of VIII:C activity or VWF:Ag.

Inhibition of VWF:RCoF activity does occur⁸ and high molecular weight multimers which possess ristocetin cofactor activity are often absent.^{6,16}

The implication is that a monoclonal (and therefore specific) antibody may bind to an area of VWF responsible for ristocetin cofactor activity. Antibody-VWF complexes appear to be rapidly cleared from the circulation.

In our case a circulating monoclonal lambda light chain presumably bound to VWF resulting in loss of high molecular weight multimers. Obvious inhibitor of VWF:Ag, VIII:C or VWF:RCoF activity in pooled normal plasma was not detected by mixing studies. Use of prednisone is felt to have suppressed production of the paraprotein. The low immunoglobulin levels in association with osteopenia and a vertebral crush fracture which developed later were suggestive of multiple myeloma despite the normal bone marrow.

Of interest, the bleeding time in our patients was normal (a finding previously reported¹³ but never satisfactorily explained). It has been postulated that this may be due to normal concentration of platelet VWF.

The association of angiodysplasia with VWS has been reported^{17,18} and was noted in our patient. It is unclear whether or not this is a chance association.

Treatment is best directed at the underlying disease as previously demonstrated in cases secondary to SLE, Wilms' tumour and myeloproliferative disorder amongst others. Specific treatment includes DDAVP, cryoprecipitate and, recently, intravenous gammaglobulin.²

Based on this case, a trial of prednisone may be indicated in patients presenting with monoclonal gammopathy and acquired VWS.

We believe this to be the first reported case of acquired VWS in association with free lambda light chains.

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