

CASE REPORT

A Teenage Boy with Systemic Lupus Erythematosus Complicated with Acquired von Willebrand Syndrome: A Rare Case and Challenging in Making Diagnosis

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ABSTRACT

In systemic lupus erythematosus (SLE), haematological abnormalities are frequent, although they are an uncommon cause of acquired von Willebrand syndrome (AVWS). AVWS is a rare condition that can cause a bleeding disorder. We presented a case of AVWS in the early diagnosis of SLE. One month before admission, the patient had a history of recurrent epistaxis. He presented to the hospital with symptomatic anaemia and was noted to have severe anaemia with iron deficiency. During hospitalisation, recurrent epistaxis recurred and was found to have prolonged activated partial thromboplastin time (aPTT), presence of lupus anticoagulant (LA), and lower von Willebrand factor (VWF), and factor 8 (VIII) levels. Simultaneously, he was diagnosed with SLE based on Systemic Lupus International Collaborating Clinics (SLICC) criteria. He underwent blood transfusions and was treated with immunosuppressive drugs such as steroids, mycophenolate mofetil, and an anti-fibrinolytic agent; he subsequently stopped bleeding and showed clinical improvement.

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INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease which may cause tissue damage in joints, skin, kidneys, and blood vessels. There are common haematological abnormalities in SLE, such as haemolytic anaemia, leukopenia, thrombocytopenia, and clotting disorders, but not for acquired von Willebrand syndrome (AVWS) (1). Acquired von Willebrand syndrome (AVWS) is a rare condition that occurs in lymphoproliferative disease, autoimmune diseases such as SLE, hypothyroidism, malignancies, or induced by drugs. AVWS is more common in adults. However, its clinical presentation and laboratory findings are similar to inherited VWD; hence it posed a clinical challenge to determine the correct type of VWD, especially in younger patients (2). Coming to the proper diagnosis is essential as the treatment modalities for both types of VWD are different. Here, we report a case of AVWS in early diagnosis of SLE in a previously healthy teenage boy.

CASE REPORT

A 15-year-old boy with no known medical history was referred to the hospital for an upper respiratory tract infection associated with recurrent epistaxis one month before admission. He also complained of dizziness, and lethargy. He denied any headaches, shortness of breath, palpitations, skin lesions, joint pain, loss of weight or appetite. He was pale, not jaundiced, mildly tachycardic, and not tachypnoeic. No bruises or mucocutaneous lesions were observed. His vital signs were stable, and other systemic studies were unremarkable. The patient is the third child in the family. He had been circumcised and undergone tooth extraction without any abnormal bleeding during his childhood. No history of bleeding or connective tissue disorder was noted in his family.

His complete blood count (CBC) revealed severe hypochromic microcytic anaemia with a haemoglobin level of 58 g/L (RR: 130-170 g/L), MCV 74 fL (RR: 83-101 fL), MCH 22.4 pg (RR: 27-32 pg), RDW-CV 18% (RR: 11.6-14%) leukopenia, $3.8 \times 10^9/L$ (RR: $4.0-10 \times 10^9/L$), and thrombocytopenia with platelet count $131 \times 10^9/L$ (RR: $150-410 \times 10^9/L$). Serum iron was deficient, 2.3 $\mu\text{mol/L}$ (RR: 10.6-28.3 $\mu\text{mol/L}$), and low transferrin saturation, calculated as 4.1%. A peripheral blood smear

suggests iron deficiency anaemia. Previously, he did not have nutritional deficiency as he had good diet history. He was transfused with one unit of packed red blood cells concurrently with intravenous (IV) iron therapy. Subsequently, after completing IV iron, his iron level was normal. His blood group is O positive, and direct Coomb's test showed a positive for auto IgG.

Further laboratory investigations revealed prolonged activated partial thromboplastin time (APTT) at 66.7 sec (RR: 21.4-36.8 sec) while the prothrombin time (PT), fibrinogen, and INR were normal. An APTT mixing study showed that immediate and 2-hours incubation were not corrected. Hence, findings suggest the presence of an immediately acting inhibitor, lupus anticoagulant (LA), or factor IX (FIX) inhibitor. Subsequent testing demonstrated a moderately present of LA and repeated LA testing after 12 weeks confirmed positive. There is a marked decrease of factor VIII (FVIII) at 2.3% (RR: 66.9%-155.3%) and a low level of FIX at 32% (RR: 60%-150%). VWF profile revealed low VWF antigen (VWF: Ag), VWF activity/Ristocetin cofactor (VWF: RCo) and FVIII coagulant antigen (FVIII:Ag) at 40.1% (RR: 52.9%-182.5%), 10.5% (RR: 59.8%-131.5%) and 2.3% (RR: 66.9%-155.3%) respectively.

The urinalysis showed proteinuria (4+), with 24-hour urine protein revealing overt proteinuria (4.51 g/day; normal level <15 g/day). However, the renal profile was unremarkable. The patient was planning for a renal biopsy, but his parents did not consent. He was positive for lupus anticoagulant (LA) and borderline for IgG anticardiolipin antibodies (ACL: 25.23 GPL; normal level < 20.00 GPL) with a normal level of IgM ACL (< 20.00 MPL) and negative for anti- β 2-Glycoprotein 1 (anti- β 2-GP1). Subsequently, antinuclear antibody (ANA) testing showed a positive reaction at dilution > 1:640 with a speckled and homogeneous appearance and tested positive for qualitative testing for double-stranded DNA (dsDNA). His C3 level was normal (0.10 g/L; normal level 0.80-1.70 g/L) and C4 level was low (< 0.01 g/L; normal level 0.12-0.36 g/L). Based on Systemic Lupus International Collaborating Clinics (SLICC) classification criteria, these results were compatible with systemic lupus erythematosus (SLE) (3).

Unfortunately, he had two episodes of epistaxis and haemoptysis on day seven of admission, soaking five small towels with fresh and clotted blood. He was then referred to the otorhinolaryngology (ORL) team, who performed an examination under anaesthesia (EUA) for nasal packing. Intraoperatively, there was intranasal mucosa bleeding; blood oozing from the sphenoidal recess; ostiomeatal complex patent; clear pharyngeal recess; and no anatomical abnormality causing bleeding or dilated vessels. On day six, the nasal packing was removed post-EUA, and there was no bleeding from the nasal or oral cavity.

As VWF: Ag level was less than 50%, with presence of epistaxis, and VWF: activity/VWF: Ag ratio < 0.7, these results are consistent with type 2 VWD. For confirmation of the subtype of VWD type 2 (2A/2B/2M/2N), we need to send further testing; VWF: Collagen binding (CB), multimer analysis, VWF: FVIII binding or genetic testing for confirmation of diagnosis. From the VWF profile above, the level of FVIII < VWF: Ag, assuming that this patient can classify as VWD type 2N. Unfortunately, all the testing mentioned above is unavailable in Malaysia's reference laboratory. Hence, based on the clinical and laboratory findings, the patient was diagnosed with SLE, and antiphospholipid syndrome (APS) complicated by AVWS.

The patient underwent multiple blood transfusions (a total of ten units of packed red blood cells, two units of fresh frozen plasma (FFP), and two units of platelet) and was treated with oral tranexamic acid to control the bleeding symptoms. Furthermore, he was treated with immunosuppressive drugs such as steroids, intravenous (IV) methylprednisolone 500mg per day for three days, then daily maintenance of 60 mg per oral prednisolone, mycophenolate mofetil and hydroxychloroquine. He responded well to the treatment and was discharged in stable condition after one month of admission. After two months, he was well with no features of anaemia or bleeding, and all his laboratory values were within normal limits.

DISCUSSION

Acquired von Willebrand syndrome (AVWS) is a rare haemorrhagic disease linked to underlying lymphoproliferative, myeloproliferative, and autoimmune diseases. The clinical presentation and laboratory findings of AVWS resemble hereditary von Willebrand disease (VWD). Most patients arrive with mild-to-moderate mucocutaneous bleeding and have no personal or family history of bleeding disorder (1,2). AVWS is associated with an underlying disorder; the most common are lymphoproliferative diseases (multiple myeloma, chronic lymphocytic leukaemia, monoclonal gammopathy of undetermined significance (MGUS), Waldenstrom's macroglobulinemia) and, less frequently, myeloproliferative neoplasms, solid malignancies, and autoimmune diseases (2).

Many mechanisms have been suggested in the pathogenesis of AVWS. In autoimmune diseases such as systemic lupus erythematosus (SLE), autoantibodies directed against functional or non-functional VWF domains have been found in circulation. Inhibitors of platelet related VWF activities (antibodies) have frequently been identified. These indicate an immunologic mechanism by which VWF is removed from the bloodstream faster or interferes with its activity (2).

AVWS is diagnosed based on a thorough clinical history and identifies associated underlying causes (Figure 1). Patients with AVWS have bleeding symptoms that resemble congenital bleeding but no personal or family history of bleeding. Initial evaluation testing for VWD includes FBC to look for platelet count, PT, APTT, fibrinogen, bleeding time or platelet function assay (PFA-100), and initial VWD assay (FVIII, VWF: Ag, VWF: RCo). These tests may indicate primary or secondary haemostasis defects that cause clinical bleeding (1,2).

AVWS laboratory results are low or normal platelet count, prolonged bleeding times, normal PT, mildly prolonged APTT with low FVIII and VWF measures (VWF: Ag, functional assays, or VWF multimers). Based on ISTH guidelines (Figure 1), to diagnose VWD type 2, the VWF quantitative assay (VWF: Ag) in plasma samples is usually normal or slightly low, and a significant decrease in qualitative platelet-related activity VWF assays, VWF: RCo, and VWF collagen binding (VWF: CB) or abnormal multimer analysis. The latter are frequently lower and result in VWF: RCo/VWF: Ag ratios of less than 0.7, equivalent to type 2A or 2B VWD. Molecular testing confirms type 2B VWD while VWF: CB testing is normal in VWD type 2M. When FVIII < VWF: Ag, it can be presumed that VWD type 2N and confirmed with VWF: FVIII B or genetic testing.

Both FVIII and FIX levels were low in this case due to the presence of lupus anticoagulant (LA). LA may result in low coagulation factors when measured with an LA-sensitive reagent but normal when measured with an LA-insensitive APTT reagent or a chromogenic assay unaffected by inhibitors (4). Blood group O could account for low VWF concentrations. Several studies have linked low VWF levels to the presence of certain VWF mutations with blood group O. The biological mechanism through which ABO regulates VWF levels has not been clearly defined despite this translational significance (5). Thus, based on his bleeding manifestations, laboratory results and normalised FVIII level after 2 months follow up, he was a rare case of AVWS in conjunction with SLE. AVWD is a complex disease to diagnose, and a thorough workup should consider all data from clinical assessment and laboratory results (2).

The potentially curative approach to managing AVWS is removing the underlying condition (via surgery, chemotherapy, radiotherapy, and immunosuppressants). Therapeutic approaches for bleeding control are the administration of desmopressin acetate and FVIII/VWF concentrate. The other therapeutic choices are intravenous immunoglobulin (IVIG), recombinant activated factor VIII (rFVIIa), plasma exchange, corticosteroids, and tranexamic acid. Returning plasma levels of FVIII and VWF to reference values after prednisone therapy indicates the presence of an immune entity called AVWS in SLE (2).

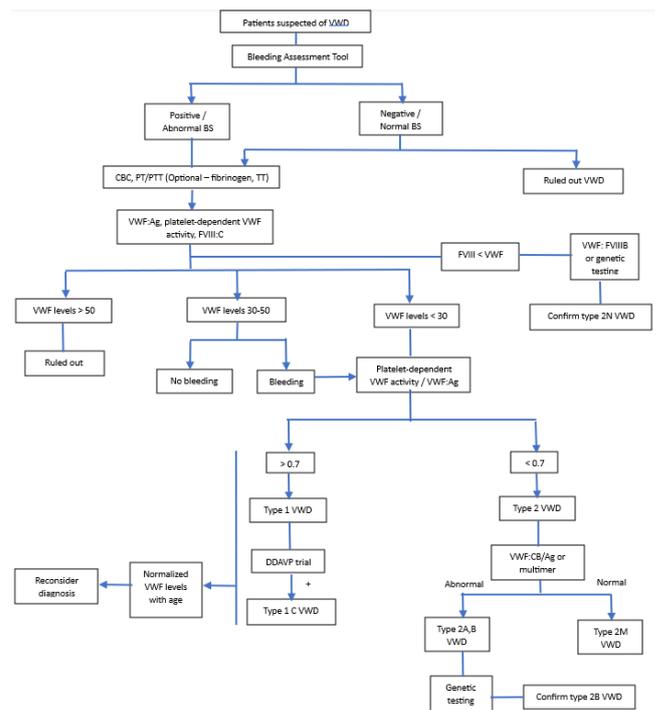


Figure 1: An algorithm addressing the diagnosis of VWD

CONCLUSION

AVWS is a complex disorder that involves complex multifactorial aetiologies. This case supports the close relationship between AVWS and SLE, as has been described previously. The diagnostic workup for AVWS is complicated. A significant element in patients with various underlying illnesses presented with bleeding without a previous history of bleeding disorders is essential for early detection and diagnosis. Effective treatment requires collaboration between haematologists, laboratory experts, and clinicians from various specialties to control the underlying diseases, reverse the coagulopathy and control the bleeding. The severity of bleeding might be influenced by the presence of multiple autoantibodies that oppose the effect of VWF deficiency, as illustrated by this case. Hence, to determine the clinical implications of this conflicting mixture of autoantibodies, more research is needed.

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