Case study of treatment responses using Privigen and Biostate with Monoclonal gammopathy of undetermined significance (MGUS) & Acquired von Willebrand syndrome (AvWS)

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Abstract: Initially described in 1968, Acquired von Willebrand syndrome (AvWS) is a rare disorder that mimics hereditary von Willebrand disease (VWD) and can be associated with life-threatening bleeding.(1) Lack of a family history of bleeding, the diagnosis of AvWS is usually based on the laboratory findings. Platelet function assay (PFA), VW antigen, VW activity, VW collagen binding activity and Factor VIII (FVIII) are used to help diagnose both acquired and inherited VWD.(2) Mechanisms of reduced VWF activity in AvWS can be either immune or non-immune. The incidence of AvWS in some populations can be greater. These include; myeloproliferative neoplasms, left ventricular assist device (LVAD), extracorporeal membrane oxygenation, autoimmune disorders, congenital cardiac anomalies or aortic stenosis, lymphoproliferative disorders, and Wilms tumour.(3)

Keywords: Acquired von Willebrand syndrome; von Willebrand factor; Biostate; Inhibitor; Monoclonal gammopathy of undetermined significance

A case study of acquired von Willebrand syndrome: We report a 61 year old male with a prolonged APTT of 60 seconds; he presented with rectal bleeding. The patient has a history of acute myeloid leukaemia and has been in remission since 1990. APTT mixing studies revealed a correction to 38 second (Refer to table 1 for reference intervals). A full investigation was performed; intrinsic factor studies revealed FVIII 15 %, FIX 170% FXI 100 % and FXII 56%. To confirm the FVIII level a Human chromogenic FVIII was performed 15%. VW antigen (VWAG) 14%, VW activity (VWAC) 10%, VW collagen binding activity (CBA) 3%. A lupus panel showed a LA ratio of 1.30 and a non-sensitive lupus APTT of 50 seconds. An inhibitor screen showed an immediate acting inhibitor, with no evidence of a time-dependent inhibitor. His antinuclear Ab screen and ENA screen were negative. A repeat sample was received and this showed FVIII of 8, VWAG of 6%, VWAC of <7 % and CBA 1 %. The patient was treated with Biostate, subsequently his von Willebrand levels quickly dropped. 20 minutes post Biostate, his FVIII levels to 56 %, VWAG to 139%, VWAC to 14% and his CBA was 62%. However, 2 hours post-Biostate, his levels were VWAG 27%, VWAC 7%, CBA 3 % and FVIII was 27%. (See figure 1) for his treatment

schedule. The serum protein electrophoresis showed an IgG kappa paraprotein that measured 3.5g/L. Figure 2 demonstrated the papaprotien in the right-sided pink peak. This was run using the CAPILLARYS 2 FLEX PIERCING | Sebia en-EN. The background immunoglobulins are markedly reduced. (Table 1).

Table 1

Immunoglobulins

IgG	IgA	IgM
6.8 g/L	0.3 g/L	0.2 g/L

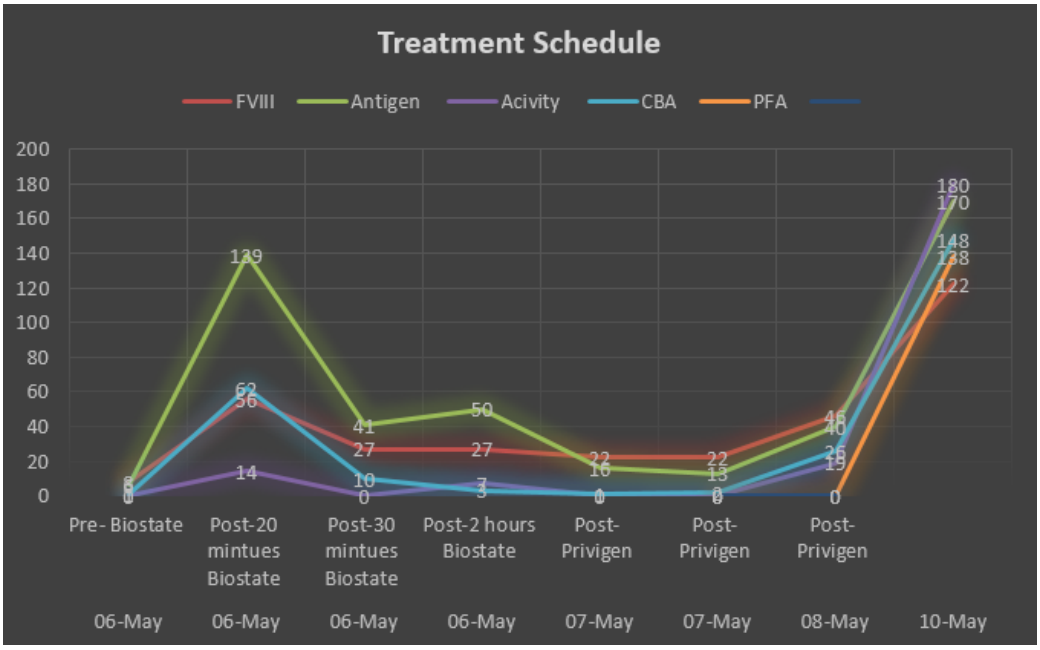

Figure 1

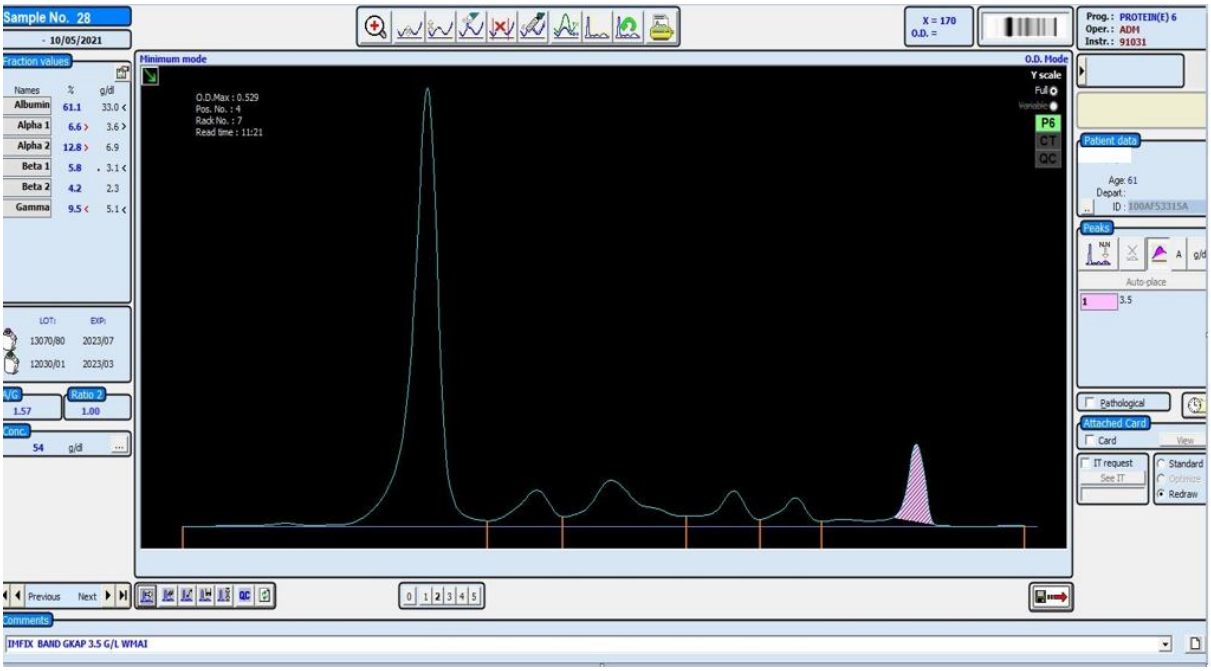

Figure 2

Table 2

Reference Intervals

Activated partial thromboplastin time (APTT), (TriniCLOT aPTT HS),	25-38 Seconds
INR (STA-NeoPTimal)	0.8-1.2
TCT (THROMBIN 10)	< 20 seconds
Fibrinogen (STA®-Liquid Fib).	1.5-5 g/L
STA® - Staclot® dRVV Screen	0.8-1.2
STA® - Staclot® dRVV Confirm	0.8-1.2
Normalized ratio = Screen ratio/confirm ratio	0.8-1.2
Non-sensitive APTT (Dade® Actin® FS Activated PTT Reagent)	25-36 seconds
STA®-ImmunoDef VIII, STA®-ImmunoDef IX & STA®-ImmunoDef XII	50-150 %
Siemens Coagulation Factor XI Deficient Plasma	70-150%
TECHNOZYM ® vWF:CBA	50-150 %
LIATEST VWF: Ag (VW Antigen)	50-150%
INNOVANCE(®) VWF Ac. Siemens (VW activity)	50-150%
IgG	7-16 g/L
IgA	0.8-4 g/L
IgM	0.4-2.5 g/L

Discussion & conclusion

The patient was diagnosed with acquired von Willebrand syndrome. The mechanism of this case's AvWS sparked much debate. He had a history of cardiac issues including atrial fibrillation and dilated cardiomyopathy. His cardiac history was a potential cause of AvWS. (5)

There have been several publications on AvWS in cardiovascular disease. "Acquired Von Willebrand Syndrome (AVWS) in cardiovascular disease: a state of the art review for clinicians" by Radha Mehta, Muhammad Athar, Sameh Girgis, Atif Hassan, and Richard C. Becker described aVWS in congenital heart disease, Aortic stenosis, Aortic Insufficiency and Mitral Insufficiency, Hypertrophic Cardiomyopathy and Ventricular Septal Defects.(5) Another possible mechanism is the lupus inhibitor. D.Hanley, Y.S.Arkel, J.Lynch, M.Kamiyama published an article on "Acquired von Willebrand syndrome in association with a lupus-like anticoagulant corrected by intravenous immunoglobulin" they reported a 47-year-old man with a prolonged APTT pre-surgery. The anticardiolipin antibody, and antinuclear antibody (ANA) were positive. Further studies revealed reduced von Willebrand factor ristocetin cofactor (vWF:RCoF), von Willebrand factor antigen (vWF:Ag), an inhibitor to vWF, and

absent high-molecular-weight vWF multimeters. After Intravenous immunoglobulin (IVIG) the APTT corrected following 7 days of IVIG treatment. (6)

However, our patient's ANA and ENA screen were negative. This makes it seem unlikely that the AvWS mechanism is a lupus inhibitor. The patient's levels of VW slowly increased with the infusion of Privigen (normal immunoglobulin). Figure 1 reflects the positive relationship between Privigen and the increasing levels of VW levels. This correlation confirmed an immune-mediated response, this ultimately excludes his cardiac issues as a cause. Interestingly, the serum protein electrophoresis showed an IgG kappa paraprotein that measures 3.5g/L. The background immunoglobulins were markedly reduced.

A study by C.Howard, APRN, T.Lin, M.Cunningham, and B.Lipe published a paper "IgGG Kappa Monoclonal Gammopathy of Undetermined Significance (MGUS) Presenting as Acquired Type III Von Willebrand Syndrome" the publication describes a patient with a 32 year history of type III VWD that was finally found to be AVWS secondary to an IgG MGUS. IV immunoglobulin was administered and much like our patient, that corrected the VW and coagulation profile. The patient they described in their study confirmed our suspicions that our patient's aVWS was secondary to the MGUS.(7)

Andreas Tiede,1 Jacob H.Rand,2 Ulrich Budde,3 Arnold Ganser,1 and Augusto B.Federici4 published "How I treat acquired vin Willebrand syndrome". In this paper they describe treatment options for AVWS include desmopressin, VWF- concentrates, recombinant factor VIIa antifibrinolytics, IVIG and plasmapheresis. Desmopressin or VWF- concentrates classically have short half-lives. Patients with IgG autoantibodies and paraproteins typically react well to IVIG. Levels generally increase after 12 to 72 hours. This can last for up to several weeks. They went on further to recommend IVIG as second-line treatment in patients who haven't responded to desmopressin or VWF-containing concentrates. IVIG takes time to take effect so using both desmopressin or VWF-containing concentrates can be required. (9) This strategy was used with our reported patient. (8) Figure 1 demonstrates the immediate effect of the Biostate along with the sharp decline, presumably the inhibitor degrading the VWF- concentrates. Privigen proved all though the second line of treatment to be more effective with providing stable levels of VWF.

The work-up of patients with AvWS is difficult, mostly because of the overlap between inherited VWD and AvWS. Prevention of bleeding with the previously mentioned treatment options along with removing when possible the underlying condition. (1) In our patient's case it isn't possible to remove the MGUS. Ultimately, maintaining control over the bleeding will be factored into his treatment pathway. Because this patient bleeds easily he has been put on regular monthly IVIG which keeps his AvWS under control. It was decided that it was less risky and more effective

than chemotherapy. The author was unable to find publications on chemotherapy and MGUS treatment with AvWS. No treatment is suggested for patients with MGUS. Monitoring MGUS is essential as risk of advancement to lymphoproliferative malignancy. (9) Our patient has been discharged from the Waikato hospital and will remain under the care of a haematologist.

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