

Von Willebrand Disease - Report of a case and review of literature

Sharanamma B* Siddarth G† Basavaraj TB‡ Pankaj J§

*M.D.S, Professor, Department of Periodontics, †M.D.S,
Reader, ‡M.D.S, Professor and Head, Dept of Oral Medicine
& Radiology, §M.D.S, Senior Lecturer, Dept of Oral
Pathology SBBDC Dental College, Gaziabad, India.
Contact:drbasavarajb@yahoo.com

Abstract:

Von willibrand's disease (vWD) is an inherited bleeding disorder with a prevalence of approximately 1% in general population. The cause for bleeding in this disorder can be attributed to the platelet adhesion abnormalities, which often happens due to the primary deficiency or defect in the von willebrand factor. The diagnosis of this disorder relies on its clinical characteristics, such as bleeding symptoms or family history of bleeding symptoms and reduced levels of von willebrand factor. We take an opportunity in reporting a patient with such rare disorder diagnosed on the basis of distinct laboratory findings and imageological studies.

Keywords: Von Willebrand disease (vWd), Von Willebrand factor(vWF), Bleeding disorder.

Introduction:

Von willebrand's disease is an inherited bleeding disorder that arises from deficiencies in the plasma protein von willebrand factor. The defect varies from quantitative to qualitative or even total deficiency of von Willebrand factor.¹

Based on the separation of vWF multimers or subunits of varying molecular weights by electrophoresis, the disorder can be sub grouped in four types. Type I accounts for approximately 85% of occurrences, with all the multimeric forms present in reduced concentrations; type II is characterized by an absence of high-molecular-weight multimers and occurs in 10 to 15% of vWd

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patients; type III (autosomal recessive inheritance) is rarely seen in homozygous individuals, characterized with less than 1% FVIII, prolonged bleeding time (> 15 minutes) and reduced level ($< 1\%$) of vWF and type IV is also known as pseudo or platelet type von willebrand disorder.² The worldwide prevalence of this disease ranges from 0.9% to 1.3%. Patients in this disease usually present with a normal platelet count, normal clotting time, normal serum fibrinogen and normal prothrombin time, but the bleeding time is increased to an extremely variable degree.³

Case Report:

A fifty-six year old male patient had come to outpatient department with complaint of bleeding gums. The patient narrated that his problem had been persistent and recurrent since childhood but from the last three months it has been more severe. Past medical history revealed that patient is known hypertensive and is under medication (tab Betalac 25mg B.D) since five years. Moreover, he had history of ischaemic heart disease and was taking medication for the same under consultation of private physician. He also had previous episodes of melaena which were recurrent and relieved on its own.



Fig. 1 Spontaneous gingival bleeding on slightest provocation

On general examination, anaemia, pallor and grade I clubbing was evident. Systemic examination of

respiratory and cardiovascular system revealed grade II dyspnoea, presence of systolic murmur, s1 and s2 sounds on auscultation respectively. Intraoral examination of the patient revealed

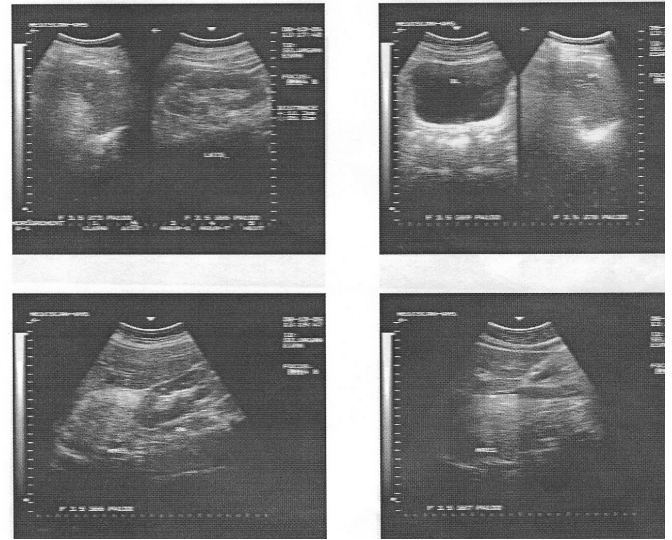


Figure 2: Abdominal ultrasound suggestive of right supra-renal mass lesion

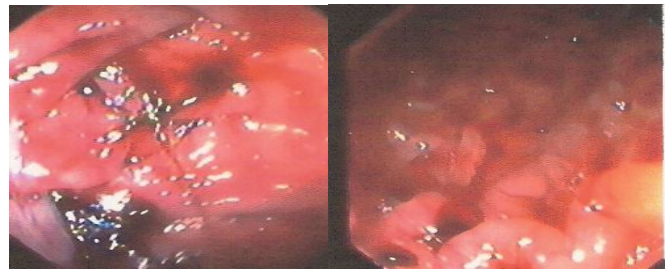


Fig.3 Lower gastrointestinal bleeding on endoscopic examination

Scintigram

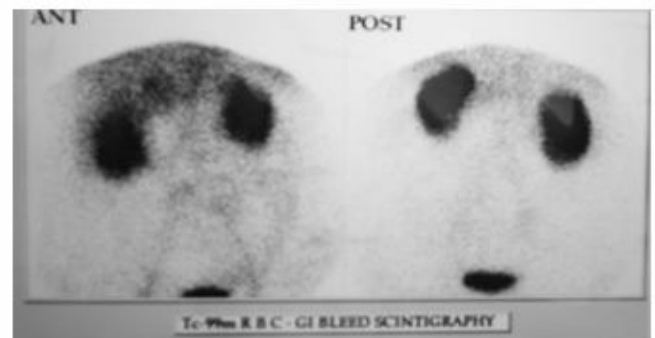


Figure4: Gastrointestinal bleeding on Scintigraphy

presence of localized periodontitis and wear facets with respect to mandibular anterior region. Soft

tissue examination of gingiva exhibited spontaneous gingival bleeding on slightest provocation (fig-1) and on palpation was soft and friable to some extent with respect to maxillary and mandibular anterior quadrant and swollen with respect to right maxillary posterior quadrant. Rest of the oral mucosa including palate and tongue were normal on inspection and palpation.

The patient was provisionally diagnosed as drug induced chronic gingival bleeding and the differential diagnosis put forth were congenital thrombocytopenia, leukaemia, idiopathic thrombocytopenic purpura and intrinsic glanzman's thrombasthenia.

The patient's consent was taken and various haematological investigations were carried out. A reduced haemoglobin percentage of 6.2gms/dl, total leukocyte count of 10,350 cells/cu mm and an increased erythrocyte sedimentation rate of 76mm/hour were markedly present. The bleeding time was prolonged notably up to 17 minutes, whereas the clotting time found out to be 8 minutes. A platelet count of 5.78 lakhs/cumm and packed cell volume of 18% was also recorded. The cytological smear revealed presence of predominantly normocytic hypochromic red cells. Many microcytic hypochromic red cells and a few macrocytic and target cells were also seen.

Amongst the biochemical assays, random blood sugar level of 101mg/dl, SGPT and SGOT of 63 and 47 units/ml was recorded respectively. A serum bilirubin level of 0.3mg/dl, total protein level of 7.0gms/dl and serum albumin of 3.3gms/dl was also recorded. Serum uric acid was found out to be 2.8mg/dl. The patient's serum was found out to be negative for Coomb's test and non-reactive for HIV and HBs Ag immuno-assays.

Patient's coagulation profile revealed a prothrombin time of 16 seconds, an elevated activated partial thromboplastin time of 37 seconds, and a thrombin time of 19 seconds. No clot lysis was observed up to a period of 2 hours while estimating euglobin clot lysis time. While screening Factor XIII, the clot was stable in 2% acetic acid. In Bethesda inhibitor assay for Factor

VIII, 0.0 Bethesda inhibitor units were present. Factor VIII c level found out to be 42.5%.

The macroscopic urinalysis examination was normal and microscopic examination revealed the presence of occasional pus cells and epithelial cells. No red blood cells, no casts and no crystals were present.

Abdominal ultrasound was done and was suggestive of presence of right supra renal mass lesion. (Fig -2) Axial sections of the chest were studied from the apices to the base of both lungs. CT chest was suggestive of right pleural effusion, Parenchymal scarring in right apex, right middle lobe and posterior basal segment of both the lower lobes. The patient was advised to undergo upper gastro intestinal endoscopy. The scope was passed up to the second part of the duodenum. Bleeding gums and bleeding from the oral cavity was evident when the endoscope passed through the pharynx and was suggestive of upper gastrointestinal bleeding. Lower gastrointestinal bleeding was profusely observed on endoscopy (Fig-3)

On sigmoidoscopy, bleeding per rectum was seen and neither polyp nor stricture, nor haemorrhoids were seen. Bleeding was evident on abdominal scintigraphy and it showed mild increased tracer concentration in the middle and distal part of descending colon which persisted from the beginning of the scintigram to an end. (Fig-4)

Following the investigatory reports, the patient was finally diagnosed as von Willebrand's disease (vWD), and on hospitalization, was given blood transfusion for severe anaemia. Intravenous infusion of an ampule of ferridiluted in 100ml N/S was administered twice in a week, altogether for a period of eight weeks. Moreover, patient was advised Tab pan 40mg once daily 1hr before food for one week, Tab folivite 5mg once weekly for 6 months, Tab neurobion forte once daily for 2 months, Cap fesorit twice daily for 4 months and Tab dolo 650mg for 2 days was given and advised to have after food.

Patient was discharged after a week and was advised bland diet and limited physical activity. His condition improved symptomatically and

haemoglobin level was also seen improving. Under 105 units of von willebrand factor cover, and slyate topical pack, the gingival bleeding was significantly reduced. On further dental visits by the patient, supra-gingival scaling and root planning was done. Patient was advised topical application of metrohexgel as a part of treatment and maintenance phase.

Patient's general health and oral hygiene was apparently normal on subsequent follow up.

Discussion:

The historical confusion that has surrounded the pathogenesis of von willebrand disease is apparent

from the many names that have been applied to this disorder. The various names that had been given to this disorder are angiohemophilia, vascular haemophilia, pseudohemophilia, constitutional thrombopathy and idiopathic prolonged bleeding time.

Erik Adolf von Willebrand first recognized the disorder in a 1926 study of the inhabitants of the Aaland Islands. Epidemiologic studies indicate that it is the most common bleeding disorder, affecting approximately 1% of the population. However, only a fraction of people come to medical and dental attention because of bleeding symptoms.⁴

A revised classification of von Willebrand disease (vWD) is as follows: ⁵

| Revised Type | Features |
|--------------|---|
| 1 | partial deficiency of vWF |
| 2A | vWF variants with loss of high molecular weight multimers and decreased platelet dependent function |
| 2B | vWF variants with loss of high molecular weight multimers caused by increased affinity for platelet Glycoprotein 1b |
| 2M | vWF variants with decreased platelet dependent function not associated with the loss of high molecular weight multimers |
| 2N | vWF variants with decreased affinity for factor VIII |
| 3 | severe deficiency of vWF |

The basic defect is a deficiency in von Willebrand factor (vWF) or abnormality of its function. vWF is required for normal platelet adhesion, and also acts as a carrier of factor VIII in the plasma. When vWF is deficient or aberrant, both factor VIII deficiency and abnormalities in the early steps of primary haemostasis result. Both of the abnormalities give rise to characteristic and distinct laboratory abnormalities, and contribute to bleeding tendency.⁶

The bleeding manifestations in vWd are heterogeneous but consistent with the dual roles of vwf in supporting both primary and

secondary haemostasis. The bleeding manifestations in the usual patient with type 1 vWD are mild, however, and many patients are virtually asymptomatic. Mucosal bleeding is particularly common. Bleeding manifestation tend to be more prominent in patients with more severe quantitative deficiency and in patients with qualitative (type2) defects. Angiodysplasia of various vascular beds, particularly those in the gut, has been observed in patients with vWD and may be an important contributory factor in chronic gastrointestinal bleeding.⁷

Diagnosis of vWD is complicated, due to both the breadth of vWF functions and the

spectrum of disorders constituting this particular entity. The large number of assays available should be considered to conclusively evaluate a patient for vWD but no test by itself is sensitive or specific enough to confirm but may provide important clues in confirming the diagnosis.³

Decisions about treatment for patients with vwd begin with accurate diagnosis and complete evaluation. The role of oral physician, in emphasizing upon seeking history of the response to hemostatic challenge such as dental extraction, tonsillectomy, surgical procedure, menstruation and peripartum hemorrhage, is of utmost importance in identifying patients with vWD.⁸ The spectrum of therapeutic interventions includes desmopressin (DDAVP) for non-exogenous replacement therapy, and adjunctive therapy with medications that modulate bleeding symptoms. To treat both the factor VIII deficiency and defect in primary hemostasis, it is generally necessary to give a product with factor VIIIc activity that also contains high molecular weight multimers of vWF.^{9,10}

Conclusion:

The early interception of this von Willebrand's disease is very much important in preventing the aggravation of the symptoms. Patients with this disease normally do not require regular treatment, but that does not indicate that they are cured, rather they are at an increased risk of bleeding all the time. The disease is passed down through families. Therefore, the role of oral health care provider in managing patients with vWd is of utmost importance as they help in minimizing the complication, expense and hazards.

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