Acquired Von Willebrand Syndrome in Chronic Myelogenous Leukemia Presenting with Severe Thrombocytosis

Deepak Chandra[a], Deepa Jayakrishnan[b], Bijay Nair[c]

a. Department of Internal Medicine, University of Arkansas for Medical Sciences, Arkansas, USA;
b. Harmony Clinic, Arkansas, USA; Little Rock Hematology/Oncology, CARTI, Arkansas, USA*

ABSTRACT

Published on 24th June 2019

Acquired von Willebrand syndrome (AVWS) is a bleeding disorder caused by acquired abnormalities in von Willebrand factor. It occurs in association with several malignant diseases as well as cardiovascular conditions. We present here the case of a woman without any family history of bleeding disorders, who presented with recurrent epistaxis from AVWS in the context of very high platelet count secondary to chronic myelogenous leukemia (CML). Her bleeding resolved with treatment of her underlying CML.

Keywords: Acquired von Willebrand syndrome, Chronic Myelogenous Leukemia, Thrombocytosis

*See End Note for complete author details

BACKGROUND

Von Willebrand factor (VWF) is a key player in primary hemostasis. It circulates as a series of multimers and the most active form are the high molecular weight fractions which provide multiple binding sites interacting with both platelet receptors and subendothelial structures at sites of injury.[1]. It also functions as a carrier for factor VIII, prolonging its half-life and protecting its clearance from circulation. Abnormalities in VWF can result in mucocutaneous bleeding such as epistaxis, melena, hematuria, petechiae and ecchymosis.

Von Willebrand disease (VWD) is a defect in synthesis or function of VWF. It was first described in 1926 by Erik von Willebrand who called it 'pseudohemophilia' because of its similarity in clinical presentation to hemophilia. He recognized the autosomal dominant inheritance pattern as opposed to the X-linked recessive inheritance seen with hemophilia. The difference in pathophysiology of these disorders was not fully elucidated until factor VIII and VWF were cloned in the 1980s.

In 1968 an acquired form of the same condition with similar clinical and laboratory manifestations was first described and is currently called Acquired von Willebrand Syndrome (AVWS). The diagnostic category of AVWS includes any structural or functional disorder of VWF associated with an increased risk of bleeding that is not inherited. One of the key aspects of the diagnostic workup is the exclusion of a bleeding history in other family members.[2]

The true incidence of AVWS is not known. It is usually associated with an underlying disorder. According to a review of 186 AVWS cases by the International Society on Thrombosis and Haemostasis Registry: malignancy such as myeloma, lymphoma, myeloproliferative disorders, chronic lymphocytic leukemia was seen in 68%, cardiovascular conditions such as states of high vascular flow including ventricular septal defect, aortic stenosis, mitral valve prolapse, ventricular assist device in 21%, and autoimmune disorders in 2%. Less commonly, AVWS has been described in hypothyroidism, uremia, hemoglobinopathies, drugs (ciprofloxacin, griseofulvin, valproic acid) and rarely without an underlying disorder.[3]. The pathophysiology of AVWS is manifold and can be mediated through immune as well as non-immune mechanisms. This may involve an acquired impairment in the synthesis or function of VWF, enhanced proteolysis, increased clearance of VWF, binding of VWF to cells etc.

Cite this article as: Chandra D, Jayakrishnan D, Nair B. Acquired Von Willebrand Syndrome in Chronic Myelogenous Leukemia Presenting with Severe Thrombocytosis. IMA Kerala Medical Journal. 2019 Jun 24;12(2):43–5.

Corresponding Author:
Dr Bijay Nair, Little Rock Hematology/Oncology, CARTI, Arkansas, USA.
E-mail: bijaypnair@gmail.com

We present here a case of acquired von Willebrand syndrome in the context of chronic myelogenous leukemia presenting with very high platelet count.

CASE REPORT

A 67 year old woman without significant past medical history presented with frequent epistaxis lasting 30 minutes to 1 hour, for a month. She was evaluated in ENT clinic and had cauterization of vessels with some temporary improvement in symptoms. She also had a complete blood count that showed a platelet count of 1.8 million/cumm, Hemoglobin was 12.7 gm/dL and WBC 13,600/ cumm with 79% neutrophils, 14% lymph, 1% monocyte, 4% eosinophils and 2% basophils. Peripheral smear revealed marked thrombocytosis, mild neutrophilia, no blasts were identified. Bone marrow aspiration and biopsy were consistent with myeloproliferative neoplasm initially thought to be essential thrombocytosis with 70-80% cellularity and increased numbers of megakaryocytes and myelocytes. The megakaryocytes showed clustering and a predominance of large hyperlobated forms. Erythroid maturation was predominantly normoblastic in the aspirate. There was a mild increase in myeloid cells predominantly myelocytes and more mature cells. There was no significant increase in blasts, promyelocytes, plasma cells nor lymphocytes. No significant collagen fibrosis was noted.

Based on initial laboratory and bone marrow findings she was started on hydroxyurea with which she did not have any appreciable reduction in platelets. In spite of her very high platelet count she was not started on aspirin because of her bleeding tendency. Later, the results of FISH (Fluorescent In-Situ Hybridization) analysis on the patient's bone marrow aspirate revealed the presence of the BCR/ABL1 gene rearrangement in 88.8% of nuclei evaluated. Cytogenetics further revealed abnormal karyotype with 18 out of 20 cells revealing (9; 22) (q34; q11.2) translocation. Polymerase chain reaction (PCR) analysis of the patient's bone marrow aspirate was negative for JAK2 V617F and MPL515 mutation which can be seen in Polycythemia Vera and Essential Thrombocytosis. Based on this additional data from molecular tests, a diagnosis of chronic myelogenous leukemia was made.

Because of her bleeding tendency a VWF profile was sent that showed deficiency in VWF activity as measured by ristocetin cofactor assay, at 27% (normal 50-170%). Antigen level was normal at 82%. VWF multimer assay was not done in her case. She did not have any family history of bleeding disorder and she has had multiple surgeries in the past that were uneventful for any bleeding complication making the diagnosis of inherited VWD unlikely.

After the results of BCR-ABL1 were available, her hydroxyurea was stopped and she was started on nilotinib at 300mg orally twice daily. Within 3 weeks of starting nilotinib, her platelet count normalized to 257,000/cumm. Her epistaxis also completely stopped in the meantime. In 6 months she attained major molecular response with < 0.1% BCR-ABL1 transcripts detected in peripheral blood by PCR.

DISCUSSION

The incidence of bleeding in the context of high platelet count is an interesting clinical paradox and can be seen in about 26% of patients presenting with essential thrombocytosis.[4] Though the main risk of high platelet count is thrombosis, the presence of a platelet count >1 million/cumm can be associated with a significantly decreased risk for thrombosis but an increased risk for bleed.[5] This is likely secondary to the occurrence of AVWS in this group of patients. AVWS has been noted in ~ 11% of patients with myeloproliferative neoplasm according to one study.[6]

In myeloproliferative neoplasms, increased platelets in circulation can bind and remove large VWF multimers from plasma. The decrease in high molecular weight multimers may be responsible for the bleeding tendency seen in patients with thrombocytosis associated with myeloproliferative diseases. Another proposed mechanism is the degradation of VWF by elastase-like enzymes from cells in the myeloid series.[7]

Treatment of AVWS in most instances involves management of the underlying clinical condition. However in case of acute bleed treatments directed specifically towards the VWF abnormality such as desmopression, VWF containing concentrates, recombinant factor VIIa, antifibrinolytics, IVIG, and plasmapheresis may be considered.

CONCLUSION

AVWS should be suspected in patients with very high platelet count who present with bleeding. In spite of the high platelet count, aspirin should be avoided in such patients. Treatment should be directed at the underlying cause. In case of acute uncontrolled bleed: DDAVP, VWF Containing concentrates, antifibrinolytics etc can be considered.

END NOTE

Author Information

1. Dr Deepak Chandra, Department of Internal Medicine, University of Arkansas for Medical Sciences, Arkansas, USA
2. Dr Deepa Jayakrishnan, Harmony Clinic, Arkansas, USA
3. Dr Bijay Nair, Little Rock Hematology/Oncology, CARTI, Arkansas, USA.

Conflict of Interest: None declared

REFERENCES

1. Ruggeri ZM, The role of von Willebrand factor in thrombus formation. Thromb Res. 2007;120 Suppl 1:S5-9.
2. Tiede A, Rand JH, Budde U, Ganser A, Federici AB. How I treat the acquired von Willebrand syndrome. Blood. 2011 Jun 23;117(25):6777-85.
3. Federici AB, Rand JH, Bucciarelli P, et al. Acquired von Willebrand syndrome: data from an international registry. Thromb Haemost 2000;84(2):345-349.
4. Tefferi A, Fonseca R, Pereira DL, Hoagland HC. A long-term retrospective study of young women with essential thrombocythemia. Mayo Clin Proc. 2001;76(1):22.
5. Carobbio A, Thiele J, Passamonti F, Rumi E, Ruggeri M, Rodeghiero F, Randi ML, Bertozzi I, Vannucchi AM, Antonioli E, Gisslinger H, Buxhofer-Ausch V, Finazzi G, Gangat N, Tefferi A, Barbui T. Risk factors for arterial and venous thrombosis in WHO-defined essential thrombocythemia: an international study of 891 patients. Blood. 2011;117(22):5857.
6. Mohri H, Motomura S, Kanamori H, et al. Clinical significance of inhibitors in acquired von Willebrand syndrome. Blood 1998;91(10):3623-3629.
7. Raife TJ, Cao W, Atkinson BS, Bedell B, Montgomery RR, Lentz SR, Johnson GF, Zheng XL. Leukocyte proteases cleave von Willebrand factor at or near the ADAMTS13 cleavage site. Blood. 2009 Aug 20;114(8):1666-74