Case Report

Evidence for Stress-induced Bleeding in a Patient with von Willebrand Factor Deficiency

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ABSTRACT

Literature reveals that psychological stress is related to hemostatic mechanisms and that excess stress can lead to prothrombotic events. Patients with chronic bleeding disorders report increased levels of subjective distress. The psychobiological link between stress and bleeding tendencies is rarely investigated when compared to the wealth of the studies on stress and clotting mechanisms. We present the case of a female with recurrent depressive disorder in whom episodic stress precipitated acute bleeding spells. An extensive hematopathological investigation revealed that she had von Willebrand factor deficiency. Our report adds to the literature that, apart from inducing procoagulant states, stress can precipitate bleeding episodes in patients with certain bleeding diatheses such as von Willebrand factor deficiency. The case also highlights that adequate pharmacotherapy and psychosocial interventions can yield adequate remission of both depression and bleeding spells.

Key words: *Bleeding, coagulation, depression, stress, von Willebrand disease*

INTRODUCTION

A growing body of evidence shows that stress and coagulatory functions are intimately related. Psychological stress precipitated by adverse life events has been implicated in inducing a hypercoagulable state.[1-3] Pathological hypercoagulability can result from heightened sympathetic activity,[4] increased platelet aggregation,[5] increased fibrin deposition,[6] or by raised levels of serum fibrinogen.[7] Nevertheless, certain observations such as increased levels of serotonin and the heightened sympathetic activity were not replicated by some studies.[8] While the studies have reported bleeding episodes to be a marker for underlying depression,[9] elevated rates of depression and anxiety have been noted in patients with bleeding problems compared to general population.[10,11]

The interplay between stress and hemodynamics continues to be complex, intriguing and may culminate in challenging clinical presentations. We present the case of a woman diagnosed with von Willebrand factor (vWF) deficiency and recurrent depressive disorder, in whom episodic exposure to psychological stress led to bleeding spells. The adequate resolution

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of depressive symptoms led to better control of the hemodynamic status.

CASE REPORT

Mrs R, a 28-year-old homemaker, hailing from a low socioeconomic background had a longstanding marital discord for 10 years. Consequently, she had multiple brief episodes characterized by sad mood and easy fatigue, which lasted for 2–3 weeks followed by a spontaneous remission without any need for hospitalization. She had made multiple suicide attempts secondary to the marital conflict. She presented with a clustering of persistent low mood, easy fatigability, somatic concern, disturbed biological functions, and suicidal ideas for 3 months. Medical history revealed episodes of abnormal uterine bleeding (AUB), epistaxis, and hematemesis during the preceding 5 months. Notably, the bleeding spells were precipitated by stressful life events and during times of significant subjective distress. The bleeding episodes subsided spontaneously without any specific treatment. There was no history of similar bleeding diathesis or a psychiatric illness in her family. The marital history revealed that her husband had alcohol dependence, which contributed significantly to their interpersonal problems. She was hospitalized due to an acute risk for suicide.

We diagnosed her with recurrent depressive disorder, current episode moderate depression without somatic syndrome as per the 10th edition of the International Classification of Diseases-Clinical Description and Diagnostic Guidelines.[12] Her baseline score on the 17-item Hamilton Depression Rating Scale (HDRS)[13] was 25. Following a suicide risk assessment, a high-risk protocol for suicide risk mitigation was initiated. Given her bleeding tendencies, amitriptyline was preferred over selective serotonin reuptake inhibitors as the antidepressant of choice and was stabilized at 50–75 mg/day along with adjunctive doses of clonazepam (1–2 mg/day). During the inpatient stay, episodes of epistaxis and hematemesis were noted. The results from endometrial cytology, indirect laryngoscopy, and an upper gastrointestinal endoscopy could not reveal any local causes for bleeding. Hence, complete hemogram and factor analyses were carried out. The patient was diagnosed to have vWF deficiency type 2. However, when the treating team identified that the bleeding spells occurred immediately post her altercations with her husband and her in-laws, the needle of suspicion pointed toward the possibility of stress-induced bleeding. The subjective distress experienced by the patient was measured using the Perceived Stress Scale (PSS). The PSS is a 10-item instrument used to measure subjective distress encountered in the past 1 month. Each item is rated on a 5-point scale ranging from never (0) to almost always (4) (total score around 13: average; ≥20: high). Positively worded items are reverse scored with higher scores indicating more perceived stress. The patient could identify that the altercations with her spouse acted as anchor points while answering the scale. The PSS scores revealed significant levels of subjective distress (mean PSS score = 32).[14] Table 1 summarizes the results of the coagulation tests. Concurrent psychosocial intervention, involving the patient and her husband, was initiated to address the marital discord. After 3 weeks of combined treatment, the depressive symptoms partially resolved (HDRS = 12). There was an improvement in the levels of subjective distress (PSS score = 16), and patient denied suicidal ideas. She was discharged and was followed up in the outpatient services. Amitriptyline (75 mg/day) and the supportive counseling sessions were continued.

However, when the couple defaulted their outpatient follow-up visits, the marital discord worsened, and the patient had bleeding episodes with a relapse of depressive symptoms and suicidal ideas. She was rehospitalized, and pharmacotherapy (amitriptyline 75–100 mg/day and clonazepam 1–2 mg/day) was restarted. Intensive counseling sessions were conducted with the patient, her husband, and other caregivers.

Table 1: Results of the hemogram and coagulation profile

Parameter	Patient's value	Normal range/control
Hemoglobin (g/dL)	13.1	11.7-15.5
Platelet count (×10³/uL)	185	150-450
Prothrombin time (s)	16.2	11.0-13.5
INR	1.22	<1.3
aPTT (s)	28.6	30.2
Coagulation profile (platelet aggregation)		
Substrate	**Patient's value (test)**	**Control**
ADP (%)	76	79
Ristocetin (%)	7	33
Epinephrine	46	71
Collagen (%)	79	64
Lupus anticoagulant test	Defective aggregation with ristocetin and normal aggregation with all agonists	
Interpretation	Suggestive of vWD/BSS	
Factor assay		
Factor	**Patient value**	**Normal range/control**
vWF:Ag (IU/dL)	72	50-150
vWF:RiCoF (IU/dL)	2	50-150
Autoimmune work up		
ANA	**Negative by ELISA**	
TSH (μIU/mL)	1.63	0.35-5.5

INR – International normalized ratio; aPTT – Activated partial thromboplastin time; ADP – Adenine di-phosphate; vWD – von Willebrand's disease; BSS – Bernard–Soulier syndrome; vWF: Ag – von Willebrand factor antigen; RiCoF – Ristocetin cofactor; ANA – Antinuclear antibody; TSH – Thyroid-stimulating hormone; ELISA – Enzyme-linked immunosorbent assay

During these sessions, the biopsychosocial model of illness, need for treatment compliance, relaxation strategies, and healthy lifestyle education (including meditation) were discussed. The patient was subsequently discharged and followed up for 6 months with no depressive or bleeding recurrences. Informed consent was obtained for the clinical management and write-up of the report.

DISCUSSION

The present case reveals that patients with heritable bleeding diatheses are more prone for stress-induced worsening of their bleeding tendencies. von Willebrand disease (vWD) is an inherited bleeding disorder and can occur either due to the quantitative deficiency of vWF (Types 1 and 3) or the qualitative deficiency of vWF (Type 2).[15] our patient was diagnosed with vWF deficiency type 2 as she had normal levels of vWF but poor platelet-mediated functions (RiCoF <2%). The patient had bleeding manifestations whenever she was subjected to significant distress due to stressful life events. Recent literature sheds light on the bidirectional link between psychological distress and bleeding. Patients with bleeding disorders report greater depressive symptoms due to various psychosocial stressors.[16,17] Conversely, patients with mental distress comorbid with cardiovascular conditions had increased chances of hemorrhage when warfarin was prescribed.[18] A recent report showed that episodic exposure to stress could precipitate bleeding episodes.[19] However, our report adds to the literature that patients with heritable bleeding diatheses such as vWD could be more prone to such stress-triggered bleeding episodes. The episodic bleeding spells could be due to stress-mediated endothelial dysfunction.[15,17] Early identification of psychological antecedents of bleeding episodes and addressing the psychosocial stressor brought an adequate improvement as revealed by the change in scores on HDRS and PSS.

Clinicians should exert considerable caution in evaluating and managing comorbid heritable bleeding diatheses and depression. Apart from pharmacotherapy, adequate psychosocial interventions in identifying and managing the cardinal psychosocial stressor are invaluable in managing such comorbid states. The future studies are necessary to identify the neurobiological underpinnings linking stress and bleeding disorders and to formulate robust pharmacotherapeutic recommendations for managing stress-related bleeding diatheses.

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Conflicts of interest
There are no conflicts of interest.

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