International Journal of Advances in Medicine
Gupta R et al. Int J Adv Med. 2022 Oct;9(10):1060-1063
http://www.ijmedicine.com
pISSN 2349-3925 | eISSN 2349-3933
DOI: https://dx.doi.org/10.18203/2349-3933.ijam20222406

Case Report

Challenges in diagnosis and management of acquired factor V inhibitors

Ruchi Gupta[1], Dinesh Chandra[1], Sanjeevan Sharma[2], Priyanka Mishra[3]*

[1]Department of Hematology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India
[2]Department of Hematology, Command Hospital, Lucknow, Uttar Pradesh, India
[3]Department of Hematopathology, Command Hospital, Lucknow, Uttar Pradesh, India

Received: 26 July 2022
Accepted: 03 August 2022

***Correspondence:**
Dr. Priyanka Mishra,
E-mail: priyanka9581@gmail.com

ABSTRACT

Inhibitors to factor V is a rare phenomenon with varied clinical presentation ranging from asymptomatic states to life-threatening bleeds. They are known to be associated with exposure to bovine thrombin, drugs, autoimmune diseases and malignancies. Establishing the diagnosis of FV inhibitors is challenging and the presence of lupus-like properties of the inhibitor can further complicate the diagnosis. Here we document an unusual case of an asymptomatic elderly female posted for pacemaker implantation and incidentally, the laboratory workup revealed a disproportionately abnormal coagulation screen. The intricacies in the diagnosis and management are discussed along with a brief review of the literature. An awareness of the diverse manifestations of this underrecognized disorder and difficulties in management is essential for medical practitioners, particularly in patients with idiopathic severe bleeding diathesis.

Keywords: Factor V inhibitor, Lupus-like inhibitor, Acquired, Idiopathic, Anti-coagulant effect

INTRODUCTION

Factor V inhibitors are rare and may occur in a patient with FV deficiency or as acquired inhibitors in an individual with no previous history of FV deficiency. The clinical presentation of acquired FV inhibitors is very diverse varying from asymptomatic states to life-threatening bleeding manifestations.[1] There is a wide array of underlying etiologies such as surgical procedures, bovine thrombin use, drugs, autoimmune disorders, malignancies and infections. However, in around 20% of cases, the cause remains unidentified.[2,3]

The factor V inhibitors can be diagnosed by performing inhibitor screen in patients with prolonged prothrombin time (PT) and activated partial thromboplastin time (APTT) followed by Factor V assay and Bethesda assay.[4] However, these inhibitors can pose a diagnostic challenge at times when they possess lupus anti-coagulant like effects acting against multiple coagulation factors.[5] We report here an intriguing case of a 56 years old lady with acquired FV deficiency, who was successfully managed with immunosuppressants. Informed consent of the patient was taken for publishing this manuscript.

CASE REPORT

A 56 years lady, diagnosed case of hypertension and dilated cardiomyopathy, presented to the haematology department of a tertiary care centre for pre-operative workup of pacemaker implantation. The patient was on multiple drugs which included aspirin, clopidogrel, metoprolol, ramipril and frusemide.

Investigations revealed prolonged PT (test- 41.9 s, control- 12.8 s) and APTT (test- 128 s, control- 28-33 s) with normal thrombin time (20s, control- 15-21 s) and increase fibrinogen (686 mg/dl, normal- 150-400 mg/dl). The patient was asymptomatic and did not provide a history of any bleeding manifestations, thrombotic episodes or anticoagulants in the past. She was multiparous with an uneventful obstetric history. General physical and

systemic examination did not reveal evidence of any bleeding manifestations, or organomegaly. Complete blood count revealed mild anemia (Hb-9.5 g/dl) with normal total leukocyte count (4500/µl), and platelets (352×103/µl). Liver function tests and renal function tests were within normal limits. In view of prolonged PT and APTT, a mixing study was performed with normal pooled plasma (1:1 ratio); there was no correction of PT and APTT, suggesting the presence of an inhibitor. Screening for lupus anticoagulant (LA) was done by using dilute Russel Viper screen and confirming tests were indeterminate as the test samples did not clot. In view of a positive inhibitor screen and indeterminate tests for LA, one-step clotting based factor assays were performed which revealed low factor X (17%), factor V (2%) and factor VIII activity (1%).

Since the levels of multiple factors were reduced, and there was no past history of any bleeding diathesis, a possibility of acquired factor inhibitor was considered. Hence factor assays were repeated after preparing serial dilutions of the test plasma with pooled normal plasma, which showed correction of factor X and factor VIII activity at higher dilutions, (1:64); however, factor V activity was consistent low (3%). This confirmed the diagnosis of acquired factor V inhibitor. Bethesda assay done for quantitation of factor V inhibitor revealed a titre of 258 Bethesda units (BU).

The evaluation for autoimmune disorders, malignancies, lymphoproliferative disorders, monoclonal gammopathy and chronic infections was negative. She was started on oral methylprednisolone (MP) 1 mg/kg with weekly monitoring of PT and aPTT. There was no improvement in coagulation profile after 3 weeks of MP therapy. After three weeks of MP, the patient has treated with Inj Rituximab 500 mg once a week for 4 doses and the MP was tapered off. After the second dose of rituximab, her PT and aPTT prolongation improved, and by the 4th dose of rituximab, the coagulation profile completely normalized. She underwent the pacemaker implantation uneventfully and her coagulation profile remained within a normal limit in the next 3 months follow up.

DISCUSSION

Acquired factor V deficiency is a rare hemostatic defect seen presenting in middle-aged adults with male predominance. A previous systematic review by Franchini et al reported bleeding manifestations in 81% of patients with involvement of multiple sites simultaneously in approximately one-third of the affected.[2]

Genito-urinary and gastrointestinal are the commonest bleeding sites, however, life-threatening intracranial haemorrhage and retroperitoneal hematomas may occur.[3] However, isolated laboratory abnormalities without bleeding manifestations or thrombosis are seen in 20% of cases as seen in our case.[2,3] Rarely antibodies may cause isolated inhibition of the anti-coagulant function of factor V leading to impaired proteolysis of factor VIIIa (activated factor VIIIa) by the Va (activated factor Va), activated protein C and protein S complex. These patients present with thrombotic complications and have lupus-like manifestations.[5-7]

The underlying aetiology is diverse with the majority of the studies citing previous exposure to bovine thrombin during surgeries as the commonest cause. Our patient was on multiple drugs for hypertension and an exhaustive workup for plausible aetiology as mentioned earlier was negative. Franchini et al carried out a systemic review of the clinicopathological profiles of 78 patients with acquired FV inhibitors, the findings of which have been summarized in Table 1.[2]

Table 1: Summary of the clinic-pathological characteristics of patient with factor V inhibitors.[2]

Characteristics	Summary
Median age of presentation (years)	69 (3-91 years)
Gender (male:female)	2:1
Presentation	
Bleeding	81
Asymptomatic	19
Sites of bleeding	
Multiple sites bleeding	32
Mucous membranes (gastrointestinal, genitourinary and airway tracts)	62
Hematuria	32
Gastrointestinal	19
Postsurgical bleed	16
Hematomas	11
Intracranial	8
Retroperitoneal	5
Etiologies with development of factor V inhibitors	
Antibiotics (b-lactams, streptomycin, cephalosporins, tetracyclines and ciprofloxacin)	42
Surgical procedures	31

Continued.

Characteristics	Summary
Infections	23
Bacterial infections	72
Viral infections	28
Malignancy	22
Solid malignancy	88
Hematological malignancy	12
Idiopathic	21
Autoimmune disorders	13
Median inhibitor titer	19 BU (0.5-1500 BU)
Median factor V activity	1 (1-20)
Management of factor V inhibitors	Observation
Asymptomatic bleeding	
Fresh-frozen plasma, platelet transfusions, prothrombin complex concentrates	
Recombinant activated factor VII (rFVIIa)	
Plasmapheresis and immunoadsorption	
Plasmapheresis and chemotherapy Intravenous immunoglobulin (IVIG)	
Immunosuppressive regimens with corticosteroids alone or in association with cyclophosphamide or other immunosuppressants	
Anti-CD20 monoclonal antibody rituximab	
Outcome of acquired factor V inhibitors	
Death	14
Inhibitor disappeared	69
Spontaneous	23
Eradication therapy	77

The laboratory abnormality in factor V inhibitors is a prolonged PT and APTT with a normal thrombin time (TT) and a normal or mildly elevated fibrinogen level. Differential diagnosis at this stage would probably be suggestive of a factor deficiency of the common pathway. However, there is no correction of PT and APTT on immediate mixing and after incubating with NPP for 1 hour and 2 hours. The factor V inhibitors are immediately acting and if present becomes evident up to 15 minutes of incubation.[4] Thus, Ashizawa et al observed a coagulation factor deficiency type pattern on mixing study but subsequent repeat tests demonstrated incubation dependent prolongation.[8] Rarely as in our case, factor V inhibitors demonstrate lupus anticoagulant like activity and inhibit multiple factors. In such cases, dilution with NPP normalizes the levels of these factors, however, the FV levels remain low.[4,5,8] Another differential diagnosis, in this case, could be lupus anticoagulant, however, despite a deranged DRVVT-screen), there was no correction of DRVVT after the addition of excess phospholipids (DRVVT-confirm). Hence a possibility of LA was excluded. Other differential diagnoses like vitamin K deficiency, liver dysfunction, disseminated intravascular coagulation and anticoagulant therapy should also be ruled out in such cases.

In the majority of the previous studies, inconsistency of low FV levels/ inhibitor titer and the severity of bleeding has been documented. Our patient remained asymptomatic despite a residual factor V activity of 2% and a high inhibitor titer of 258 BU.[2,3] A probable explanation for this phenomenon is the platelet factor V stored in megakaryocytes in a partially active state and resistant to inhibition by these autoantibodies that usually target the C2 epitope of factor V binding to phospholipids.[9]

The management of factor V inhibitors encompasses control of bleeding and the eradication of inhibitors. Asymptomatic patients may or may not require inhibitor eradication therapy, while in symptomatic patients, fresh frozen plasma, prothrombin complex concentrates, recombinant activated factor VII and platelet transfusions have shown variable outcomes with response in 35-71% of cases.[2] Immunosuppressive agents like corticosteroids with or without cyclophosphamide and rituximab have been successful in 80% of cases.[10,11] The remission rates were maximum in idiopathic cases and least with the worst prognosis in autoimmune disorders and malignancies.[2]

CONCLUSION

The uniqueness of this case is the unusual laboratory abnormalities resulting from inhibition of multiple coagulation factors and LA like properties of the inhibitor, which resulted in a diagnostic dilemma. The importance of performing factor assays in dilution cannot be underscored in such cases. Awareness of the properties of such inhibitors is important to achieve a correct diagnosis and prompt intervention.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Ang AL, Kuperan P, Ng CH, Ng HJ. Acquired factor V inhibitor. A problem-based systematic review. Thromb Haemost. 2009;101(5):852-9.
2. Franchini M, Lippi G. Acquired factor V inhibitors: a systematic review. J Thromb Thrombolysis. 2011;31(4):449-57.
3. Wiwanitkit V. Spectrum of bleeding in acquired factor V inhibitor: a summary of 33 cases. Clin Appl Thromb Hemost. 2006;12(4):485-8.
4. Kamal AH, Tefferi A, Pruthi RK. How to interpret and pursue an abnormal prothrombin time, activated partial thromboplastin time, and bleeding time in adults. Mayo Clin Proc. 2007;82(7):864-73.
5. Wang L, Nguyen A. Acquired factor V inhibitor with lupus-like features. Lab Med. 2002;33(9):551-2.
6. Kapur A, Kelsey PR, Isaacs PE. Factor V inhibitor in thrombosis. Am J Hematol. 1993;42(4):384-8.
7. Perdekamp MT, Rubenstein DA, Jesty J, Hultin MB. Platelet factor V supports hemostasis in a patient with an acquired factor V inhibitor, as shown by prothrombinase and tenase assays. Blood Coagul Fibrinolysis. 2006;17(7):593-7.
8. Ashizawa M, Kimura S, Wada H, Sakamoto K, Sato M, Terasako K, et al. Acquired factor V inhibitor associated with life-threatening bleeding and a mixing test result that indicated coagulation factor deficiency. Hematology. 2013;18(5):300-4.
9. Gould WR, Simioni P, Silveira JR, Tormene D, Kalafatis M, Tracy PB. Megakaryocytes endocytose and subsequently modify human factor V in vivo to form the entire pool of a unique platelet-derived cofactor. J Thromb Haemost. 2005;3(3):450-6.
10. Lebrun A, Leroy-Matheron C, Arlet JB, Bartolucci P, Michel M. Successful treatment with rituximab in a patient with an acquired factor V inhibitor. Am J Hematol. 2008;83(2):163-4.
11. Takemoto K, Hamada O, Kitamura K, Fujiwara N, Miyakawa Y. Challenges in management of unusual acquired factor V deficiency: A case report. Medicine (Baltimore). 2019;98(17):e15259.

Cite this article as: Gupta R, Chandra D, Sharma S, Mishra P. Challenges in diagnosis and management of acquired factor V inhibitors. Int J Adv Med 2022;9:1060-3.