Ann Biol Clin 2020; 78 (2): 206-9

Haemodialysis Tunisian patient with acquired factor V inhibitor associated to arteriovenous shunt thrombosis

Anti-facteur V acquis et thrombose: à propos d'un cas et revue de la littérature

Ikbel Ghachem[1]
Wijdène El Borgi[1,2]
Sarra Fekih Salem[1,3]
Fatma Ben Lakhal[1,2]
Amel Chelbi[4]
Iheb Ghiriani[5]
Emna Gouider[1,2]

[1] Laboratoire d'hématologie, Hôpital Aziza Othmana, Tunis, Tunisie

[2] Université El Manar, Faculté de médecine, Tunis, Tunisie

[3] Faculté de Pharmacie de Monastir, Tunisie

[4] Biologiste de libre pratique

[5] Gériatre de libre pratique

Article received December 23, 2019, accepted March 06, 2020

Abstract. Factor V deficiency is a rare hemostatic disorder. It may present with a diverse spectrum of symptoms due to a variety of mechanisms including development of autoantibodies associated with a number of conditions. We report a first case of factor V deficiency in Tunisian hemodialysis patient due to an autoantibody most likely secondary to antibiotic exposure responsible for an arteriovenous shunt thrombosis rather than bleeding. We discuss here the clinical and biological features of acquired factor V inhibitor and provide a short review of the current literature.

Key words: *acquired factor V inhibitor, thrombosis, haemodialysis, biological tests*

Résumé. Le déficit en facteur V est un trouble de l'hémostase rare associé à des difficultés diagnostiques. La présentation clinique est cependant variable en raison de divers mécanismes impliqués, notamment le développement d'autoanticorps associés à un certain nombre de conditions. Nous rapportons un premier cas de déficit en facteur V chez un patient tunisien hémodialysé en raison d'un auto-anticorps probablement dû à une exposition à un anti-biotique responsable d'une thrombose de la fistule artério-veineuse plutôt que d'un saignement. Nous discutons ici de la manifestation inhabituelle et des caractéristiques biologiques de l'inhibiteur du facteur V acquis et dressons un bref aperçu sur la littérature actuelle.

Mots clés : *anticorps anti-FV acquis, thromboses, hémodialyse, tests biologiques*

Acquired factor V inhibitor (AFV-I) is a rare haemostatic disorder characterized by the presence of an autoantibodies or alloantibodies against coagulation factor V [1]. Clinical manifestations are variable and range from asymptomatic laboratory abnormalities to bleeding disorders or even thrombotic events [2]. The diagnosis is purely biologic and often difficult and may be confused sometimes with others inhibitors [3]. Herein we report a case of AFV-I in haemodialysis Tunisian patient who developed thrombosis in the arteriovenous shunt.

Case report

This is a 75 years-old Tunisian patient with kidney failure in haemodialysis stage hospitalized for an arteriovenous shunt creation. He has no personnel or familial history of haematological disorders. At admission, complete blood count showed haemoglobin of 8.5g/dl with a normal white blood cells and platelets count. Prothrombin time (PT) and activated partial thromboplastin time (aPTT) were normal. During his hospitalization, the patient presented a urinary infection treated with cefotaxime 1gx3/day and developed a thrombosis on the haemodialysis puncture site. His PT and aPTT were prolonged (PT=37.3 s, ratio= 2.84 and aPTT=79.6 s, ratio=2.65). The mixing study with normal plasma (1:1) showed a total correction of the PT and aPTT.

Correspondence : I. Ghachem
<ikbel-ghachem@hotmail.com>

doi:10.1684/abc.2020.1540

To cite this article: Ghachem I, El Borgi W, Fekih Salem S, Ben Lakhal F, Chelbi A, Ghiriani I, Gouider E. Haemodialysis Tunisian patient with acquired factor V inhibitor associated to arteriovenous shunt thrombosis. *Ann Biol Clin* 2020; 78(2): 206-9 doi:10.1684/abc.2020.1540

Table 1. Comparison of coagulation tests before and after 1h of incubation (37°C).

Test (time in second)	PT		aPTT		TT	DRVVT Screen	DRVVT Confirm
	Before incubation	After 1h of incubation	Before incubation	After 1h of incubation			
Normal plasma	13.1	12.6	30	32.9	14.9	35.6	30.2
Patient	37.3	41.2	79.6	116	17.9	132.8	>121
Ratio	2.84	1.3	2.65	3.52	-	3.73	>4
Mixture study (1:1)	-	16.4	34.3	40	-	40.6 (ratio=1.14)	33.3 (ratio=1.1)

PT: prothrombine time, aPTT: activated partial thromboplastin time, TT: thrombin time, DRVVT: dilute russel viper venom time.

Thrombin time (TT) was normal. No bleeding symptoms were detected. Liver function was normal. After incubation for 1 hour at 37°C, the Rosner Index was 6%. Fibrinogen level was 5.88 g/L. After ruling out common causes of a combined prolonged PT and aPTT including disseminated intravascular coagulation and chronic liver disease, we performed specific factors assays. Factors X, VII and II activities were 129%, 117% and 90%, respectively. Factor V level was markedly reduced to 4% but increased at different dilution suggesting the presence of an inhibitor rather than a factor deficiency. Screening for lupus anticoagulant (LA) using the diluted russel viper venom time (DRVVT) was negative. The DRVVT screen lengths unusual the clotting time but the inhibitor was not lipid dependent (*table 1*). An AFV-I was screening using the algorithm approach proposed by Sridharan *et al*. [4] who used the ratio 4 part patient plasma to 1 part normal pool plasma to increase the sensitivity of FV inhibitor detection which was positive and confirmed later by classical Bethesda method revealing 2 BU titer. Underlying disease like neoplasia or autoimmune pathology was absent. One week after stopping antibiotic therapy, coagulation assessment was normal.

Discussion

AFV-I is a rare disease but may be underestimated because undiagnosed [5]. To our knowledge, this is the first African case reported. The clinical presentation is variable, most patients present with haemorrhage while some others are asymptomatic or have rarely thrombosis complications [2, 6-10]. Many mechanisms could explain the heterogeneous clinical presentation.

In fact, AFV-I can recognize the epitope in the C2 domain of light chain of FV which mediates the binding of the activated FV to phospholipids membranes resulting in loss of FV affinity for factor Xa, which reduces the efficiency of conversion of prothrombin to thrombin and therefore are more likely responsible of bleeding symptoms [2, 14].

AFV-I may also inhibit the anticoagulant effects of FV leading to thrombosis. FV-I associated with thrombosis have been documented in 9 previous case reports (*table 2*). The majority of thrombosis sites were deep venous thrombosis. Reports of arterial thrombosis are extremely rare such us our case report [6, 10]. FV inhibitor can lead to procoagulant diathesis by indirectly inhibiting the inactivation of FVIIIa by activated protein C/protein S complex and by directly inhibiting the inactivation of FVa but neither PT, aPTT will be affected in this case [11].

Most common form of factor V auto-antibodies are associated with a number of condition including mostly antibiotics (38%), surgery (29%) and infection (27%) [12, 13]. The present patient's clinical examination and medical history did not show bovine thrombin exposure, malignancies or autoimmune diseases. However, he was exposed to cefotaxime for the treatment of urine infection. This antibiotic is specifically of the β-lactam group associated the most frequently with the development of AFV-I [1]. Discontinuation of the antibiotic therapy normalized the PT and aPTT.

For the last 10 years, the most cases of AFV-I associated with antibiotic condition were noted in asymptomatic and bleeding patients (*table 3*). Only one case of AFV-I associated with B-lactam and ciprofloxacin treatment was reported responsible for deep vein thrombosis [15].

In systematic reviews, there are 3 cases of patients suffered from kidney failure associated with eosinophilia and AFV-I. One case was undergoing haemodialysis as our patient and the two others have membranous nephropathy, suggesting an underlying immuno-allergic process [16, 17].

For laboratory finding, all documented cases were consisting with a prolonged PT and aPTT. The TT is usually normal; however, it can be prolonged when the patient has been exposed to bovine thrombin [12]. The mixing study results were variable. In Boland *et al.* review, 91% of cases showed no correction on 1:1 mixing studies with pool normal plasma [13]. Unlike FVIII inhibitors, FV inhibitors do not show initial clotting time correction with subsequent prolongation after incubation. In fact, FV-I inactivate FV almost immediately to 15 minutes in vitro upon mixing [6, 18]. Only four cases, were fully corrected and represent then a rare entity like our case which contradicts with the basic principal of coagulation factors inhibitors

Table 2. Acquired factor V inhibitors in thrombosis: analysis of literature data.

Reference	Gender/ age	Thrombosis site	Drugs/ condition	FVa (%)	Inhibitor titre (UB)	Treatment	Outcome/time of disappearance of inhibitor in week
Kapur (1993) [6]	F/68	Thrombosis lumb gangrene	No	<1	144	VK, FFP	Remission (6 months)
Koyama 1995 [10]	M/74	Cerebral infarction	Sjogren's syndrome, gastric carcinoma	5	-	Acetylsalicylic acid	1 year
George 1995 [21]	M/66	Deep vein thrombosis	CPX	1.5	160	FFP, VK, PLT	3 weeks
Kamphuisen 1998 [7]	M/71	Deep vein thrombosis	Surgery	<3	61	Anticoagulant therapy	2 weeks
Kalafatis 2002 [11]	F/44	Deep vein thrombosis	No	102	-	Anticoagulant therapy	Inhibitor persistent
Higuchi 2012 [8]	F/82	Deep vein thrombosis	-	2	4	Steroids	2 weeks
Aljohani 2014 [22]	M/64	Deep vein thrombosis	Mantle cell lymphoma	<0.01	80	Steroids	<8 weeks
Gavva 2016 [15]	F/64	Deep vein thrombosis	B-lactam, CFX, sepsis	2	5	Steroids	<3 weeks
Rief 2016 [23]	M/58	Deep vein thrombosis	No	<8	2.65	Immuno-suppressive	2 months

CPX: ciprofloxacin, VK: vitamin K, FFP: fresh frozen plasma, PLT: platelets, M: male, F: female.

Table 3. AFV-I associated with antibiotic condition in asymptomatic and bleeding patients.

	Suspected etiology	Inhibitor titre (BU)	FVa (%)	APTT (sec)	PT (sec)	Outcome/time of disappearance of inhibitor in week
Asymptomatic	CPX	1	25	38.3	25.8	Spontaneous resolution (1 week)
Asymptomatic	Antibiotic	-	-	-	-	Remission
Asymptomatic	CPX	10	2	200	68.3	Remission (1week)
Asymptomatic	B-lactam	-	6	72	24.9	Remission (1week)
Site of bleeding						
Gastrointestinal	CPX	4	6	173	50.7	-
Haematuria	CPX	6.6	6.2	100	50	3 weeks
Epistaxis, intracerebral hemorrhage	B-lactam	-	-	120	-	-
Hematoma	B-lactam	50	<5	150	-	-
Intracranial hemorrhage		70	-	160	59.1	-
Purpura	B-lactam	11	< 2	-	-	4 weeks
Pulmonary hemorrhage	B-lactam	83	< 3	-	-	-

CPX: ciprofloxacin, PT: prothrombine time, aPTT: activated partial thromboplastin time.

[13, 19]. According to Shridharan *et al*., screening for FV-I was made using separate mixing studies performed with 4 parts of platelet poor patient plasma and 1 part of normal plasma to sensibilize this assay after 1 h incubation of this mixture at 37°C [4]. The Bethesda assay confirms the presence of a FV-I with a titer of 2 UB which hypothesized that FV-I is not active at ambient temperature and may be time dependent.

The low title of FV-I responsible for a very low FV level (4%) hypothesizes the neutralisant character of the inhibitor. According to the literature, FV- I titer ranged from 1 to 279 Bethesda units with median of 4 BU/mL. There was no correlation between inhibitor titers and/or FV activity levels and symptoms [4].

In our case, there was a diagnostic dilemma since the patient present thrombotic symptoms. LA is still involved and

distinguishing between an FV-I and LA can be challenging. Most FV-I didn't show LA activity in modern assays. However, some puissant FV-I could interfere and prolonged the DRVVT screen, but the DRVVT confirm will be typically not correct after addition of excess phospholipid. Although some FV-I could have LA-like properties and induced frequently thrombosis complications. In that case, multiple coagulation factors will appear to be suppressed and though FV may be suppressed out of proportion to the others [20]. The second dilemma was the short time for inhibitor disappearance (1 week). In systematic reviews, the kinetic of disappearance was documented with a median time of 3.5 weeks with extremes between 1 to 10 weeks [13]. Unfortunately, we were not able to monitor closely the patient because he was in another institution in the private sector and we did not screen again for inhibitor in other samples.

Conclusion

This case report illustrates the big dilemma of unusual clinical and biological features with unclear etiology. It is important to remember that FV inhibitors may not behave clinically like other coagulation factor inhibitors and may be associated with thrombosis rather than bleeding. Additional studies are required to elucidate this association. Unexplained prolongations of the PT and aPTT with a correction in a mixing test with a normal TT should not exclude an inhibitor and require always a diagnostic investigation. AFV-I, likely under-recognized, poses many challenges to treating physicians with limited evidence to guide its management. That's why clinical-biological cooperation remains an important step in the diagnosis of AFV-I.

Acknowledgments. Ghariani I and Chelbi A were the Doctors consultant who clinically evaluated the patient and provided the details of the case report. Ghachem I contribute the biological research and write the manuscript. Doctors Gouider E, El Borgi W, Ben Lakhal F and Fekih Salem S provided extensive reviews and editing of the manuscript.

Conflict of interest: none of the authors has any conflict of interest to disclose concerning this article.

References

1. Ogawa H, Souri M, Kanouchi K, Osaki T, Ohkubo R, Kawanishi T, *et al*. Case report a high titer of acquired factor V inhibitor in a hemodialysis patient who developed arterial thrombosis. *Int J Hematol* 2019 ; 109(2) : 214-20.

2. Ortel TL. Clinical and laboratory manifestations of anti-factor V antibodies. *J Lab Clin Med* 1999 ; 133 : 326-34.

3. Favaloro EJ, Bonar R, Duncan E, Earl G, Low J, Aboud M, *et al*. Identification of factor inhibitors by diagnostic haemostasis laboratories A large multi-centre evaluation. *Thromb Haemost* 2006 ; 96(1) : 73-8.

4. Sridharan M, Fylling KA, Ashrani AA, Chen D, Marshall AL, Hook CC, *et al*. Clinical and laboratory diagnosis of autoimmune factor V inhibitors : a single institutional experience. *Thromb Res* 2018 ; 171 : 14-21.

5. Ang AL, Kuperan P, Ng CH, Ng HJ. Acquired factor V inhibitor. A problem- based systematic review. *Thromb Haemost* 2009 ; 101 : 52-9.

6. Kapur A, Kelsey PR, Peter ET. Factor V inhibitor in thrombosis. *Am J Hematol* 1993 ; 42 : 384-8.

7. Kamphuisen PW, Haan J, Rosekrans PCM, Van Der Meer FJM. Deep-vein thrombosis and coumarin skin necrosis associated with a factor V inhibitor with lupus-like features. *Am J Hematol* 1998 ; 57(2) : 176-8.

8. Higuchi T, Okamoto T, Kou T, Takeuchi T, Koyamada R, Okada S. Deep vein thrombosis associated with factor V inhibitor followed by immune thrombocytopenia. *Ann Hematol* 2012 ; 91(11) : 1831-2.

9. Olson NJ, Ornstein DL. Factor V inhibitors: a diagnostic and therapeutic challenge. *Arch Pathol Lab Med* 2017 ; 141(12) : 1728-31.

10. Rief P, Hackl G, Hafner F, Raggam RB, Wölfler A, Brodmann M, *et al*. Venous thromboembolism in a patient with persistent inhibitor to coagulation factor V – a case report. *Clin Chem Lab Med* 2016 ; 54(9) : e269-71.

11. Kalafatis M, Simioni P, Tormene D, Beck DO, Luni S, Girolami A. Isolation and characterization of an antifactor V antibody causing activated protein C resistance from a patient with severe thrombotic manifestations. *Blood* 2016 ; 99(11) : 3985-93.

12. Franchini M, Lippi G. Acquired factor V inhibitors : a systematic review. *J Thromb Thrombol* 2011 ; 31 : 449-57.

13. Boland F, Av S. Acquired factor V inhibitors: a review of literature. *Ann Hematol Oncol* 2017 ; 4(9) : 1168.

14. Ortel BTL, Moore KD, Quinn-allen MA, Okamura T, Sinclair AJ, Lazarchick J, *et al*. Inhibitory anti-factor V antibodies bind to the factor V C2 domain and are associated with hemorrhagic manifestations. *Blood* 2019 ; 91(11) : 4188-96.

15. Gavva C, Yates SG, Rambally S, Sarode R. Transfusion management of factor V deficiency: three case reports and review of the literature. *Transfusion* 2016 ; 56 : 1745-9.

16. Kitazawa A, Misawa H, Nagahori K, Koda R, Yoshino A, *et al*. Acquired factor V inhibitors in a patient with end-stage renal disease. *Intern Med* 2016 ; 55(23) : 3505-9.

17. Kitamura S, Misawa M, Namba S, Tsuji K, Torigoe R, Shima M, *et al*. Membranous nephropathy with acquired factor V inhibitor : a case report. *BMC Res Notes* 2013 ; 6 : 553.

18. 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 Fibrinylosis* 2006 ; 17(7) : 593-7.

19. Kang SH, Montecalvo J. Factor V inhibitor with complete correction of the PT and aPTT mixing study. *Am J ClinPathol* 2013 ; 140 : A192.

20. Wang L, Nguyen A. Acquired factor V inhibitor with lupus-like features. *Laboratory Medicine* 2002 ; 33(7) : 551-2.