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Acquired factor V deficiency in a patient with a urinary tract infection presenting with haematuria followed by multiple haemorrhages with an extremely low level of factor V inhibitor: a case report and review of the literature

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Acquired factor V deficiency (AFVD) is a rare haemostatic disorder that is primarily because of the development of factor V inhibitors. Approximately, 200 cases have been reported and the greatest portion of these cases was because of bovine thrombin exposure. We report a case of a man who presented with haematuria followed by multiple haemorrhages associated with an elevated prothrombin time and an activated partial thromboplastin time. A workup revealed reduced factor V activity and a factor V inhibitor level of 1.9 BU, which were likely secondary to a urinary tract infection. Using corticosteroids, we successfully eliminated the inhibitor and controlled the bleeding. We review the published literature to identify the conditions that are associated with nonbovine thrombin AFVD. We assume that AFVD should be kept in mind for patients who present with multiple haemorrhages. *Blood Coagul Fibrinolysis* **28:334–341**

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Introduction

Coagulation factor V is a coagulation protein that is synthesized by the liver and possibly by megakaryocytes. Factor V is present in the blood plasma as a single-chain polypeptide (80%) and in platelet α-granules (20%). Factor V participates in procoagulantion because it is a cofactor of the prothrombinase complex. Factor V also plays an important role in the anticoagulant pathway because it plays a pivotal role in haemostasis: its inactivated form participates in the inactivation of factor VIII via activated protein C (APC). Thus, factor V plays an essential role in both procoagulant and anticoagulant pathways. Factor V functional disorders can cause haemorrhagic or thrombotic events. Acquired factor V deficiency (AFVD) is a rare haemostatic disorder that is generally because of the development of antibodies against factor V. AFVD was first reported in 1955 [1,2], and there are approximately 200 case reports or case series describing this disorder in the current literature. The majority of cases of AFVD have occurred in the presence of associated risk factors that include bovine thrombin exposure during surgical procedures, antibiotic administration (especially antibiotics of the lactam group), cancers, and autoimmune disorders. The clinical manifestations of AFVD are variable and range from asymptomatic laboratory anomalies to fatal haemorrhagic or thromboembolic events. Here, we report a Chinese case of AFVD that presented with haematuria followed by multiple haemorrhages that resulted from an extremely low level of factor V inhibitor and was potentially secondary to a urinary tract infection.

Case report

Our patient was a 64-year-old man who was admitted to our hospital with a 15-day history of haematuria and a 6-day history of nose and tonsil bleeding.

The patient was previously evaluated in another hospital, and levofloxacin was prescribed with a diagnosis of cystitis. The coagulation profile revealed both a prolonged prothrombin time (PT) of 113.80 s (11–14.5 s) and an activated partial thromboplastin time (APTT) of more than 180 s (28–45 s). Haemostatic drugs were prescribed for his bleeding. However, these drugs did not correct his PT or APTT, and he subsequently developed nose and tonsil bleeding. His past medical history included prostatic hyperplasia for 10 years and a surgery after a car accident in 2011. However, he had no history of significant coagulation disorders with prior surgical procedures or other family bleeding history. He had no documented history of medicines. Upon physical examination, slight tenderness was present on epigastric palpation and kidney region percussion. Upon laboratory examination, his haemoglobin level was 105 g/l (115–150 g/l), his red blood cell count was 3.28×10^9/l ($3.8–5.1 \times 10^9$/l), his white blood cell count was 7.9×10^9/l ($3.5–9.5 \times 10^9$/l), his

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Table 1 Laboratory findings

Blood chemistry			
ALT	17 (9–50 IU/l)	K	3.78 (3.50–5.30 mmol/l)
AST	15 (15–40 IU/l)	Cl	103 (99–110 mmol/l)
GGT	31 (10–60 IU/l)		
AKP	90 (45–125 IU/l)	Serology	
LDH	270 (120–230 IU/l)	HBsAg	–
TP	73.2 (6.0–85.0 g/l)	HBsAb	–
ALB	45.2 (40.0–55.0 g/l)	HBeAg	–
TBIL	5.3 (5.0–21.0 μmol/l)	HBeAb	–
DBIL	2.1 (0.0–6.0 μmol/l)	HBcAb-IgG	–
IBIL	3.2 (2.0–15.0 μmol/l)	HCV Ab	–
BUN	5.68 (2.30–7.80 mmol/l)	HCV Ag	–
Cr	65 (262–115 μmol/l)	PreS1-Ag	–
Na	142 (137–147 mmol/l)	TP-Ab	–

AKP, alkaline phosphatase; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate transaminase; BUN, blood urea nitrogen; CYP4F2, cytochrome P450 4F2; CYP4V2, cytochrome P450 4V2; DBIL, direct bilirubin; GGT, γ-glutamyl transpeptidase; HBsAg, hepatitis B surface antigen; HBsAb, antibody to hepatitis B surface antigen; HBeAg, hepatitis B e-antigen; HBeAb, antibody to hepatitis B e-antigen; HBcAb, antibody to hepatitis B core antigen; HCV Ab, antibody to hepatitis C virus; HCV Ag, hepatitis C antigen; IBIL, indirect bilirubin; JAK2, Janus kinase 2; KLKB1, kallikrein B1; LDH, lactic dehydrogenase; PreS1-Ag, PreS1 antigen; SERPINC 1, serpin C1; TBIL, total bilirubin; TP, total protein; TP-Ab, treponema pallidum antibody; –, negative.

platelet count was 162×10^9/l ($125–350 \times 10^9$/l), and his fibrinogen was 3.98 g/l (2–4 g/l). The blood chemistry revealed no liver dysfunction (Table 1). The coagulation profile revealed both a prolonged PT of 51.70 s (11–14.5 s) and an APTT of more than 180 s (28–45 s; Table 2). His factor V activity was markedly reduced (2% of normal; Table 3). The levels of factors VII/VIII and factor IX were within the reference ranges. His blood chemistry was unremarkable. The overall results indicated the presence of antibodies against factor V and suggested a diagnosis of AFVD. A standard Bethesda assay confirmed the presence of factor V inhibitor with a low level of 1.9 BU. The patient received an infusion of fresh frozen plasma (FFP) with a partial correction of his coagulation parameters (Table 2). Subsequently, the factor V inhibitor was undetectable. However, the FFP exhibited no obvious effect on restoring the plasma factor V activity (Table 3). The patient was discharged because his bleeding stopped.

On 24 April 2015, 45 days after his initial visit, the patient was readmitted to our hospital with a 3-day history of gingival haemorrhage and haematoma of the right lower limb (Fig. 1). On examination, with the exception of the gingival haemorrhage and skin bruising on his right lower limb, the patient exhibited no other bleeding or bruising, nor was any area abnormal. A complete blood count revealed normal white blood cell and platelet levels of 8.48×10^9 and 144×10^9/l, respectively, but a reduced haemoglobin value of 67 g/l, which indicated anaemia because of blood loss. On investigation of his coagulation parameters, a prolonged PT of 63.6 s, an APTT of 188.7 s, and a marked reduction in factor V activity (3% of normal) were noted (Tables 2 and 3). We immediately administered the patient a transfusion of 2 units of red blood cells and 250 ml FFP followed by another 7 days of FFP transfusions at the dose of 200 ml/day with concurrent monitoring of PT/APTT and factor V activities. The FFP transfusion ultimately resulted in a correction of the PT/APTT values to normal limits. The factor V activity was partially corrected from 3 to 22%. A further evaluation for congenital factor V deficiency did not reveal a factor V Leiden genotype, and the evaluations of factor II, protein C, protein S, SERPINC 1, cytochrome P450 4F2 (CYP4F2), cytochrome P450 4V2 (CYP4V2), kallikrein B1 (KLKB1), and Janus kinase 2 (JAK2) mutation were normal, but a c.1538G>A (1628G>A, Arg485Lys) mutation was detected (Fig. 2). However, screening

Table 2 Prothrombin time and activated partial thromboplastin time results after the first and second admissions

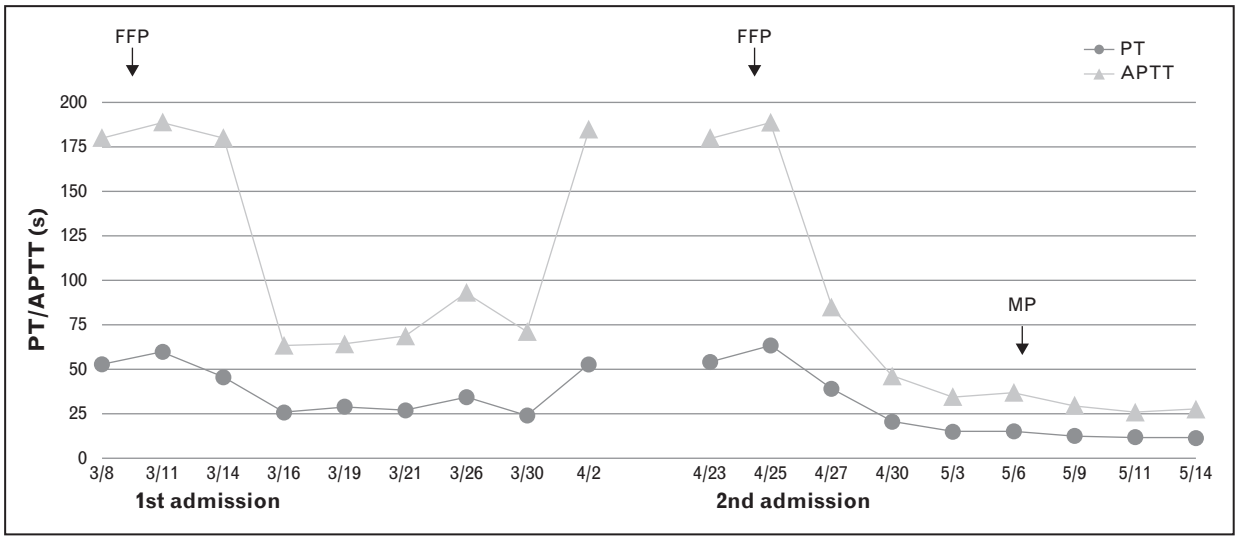
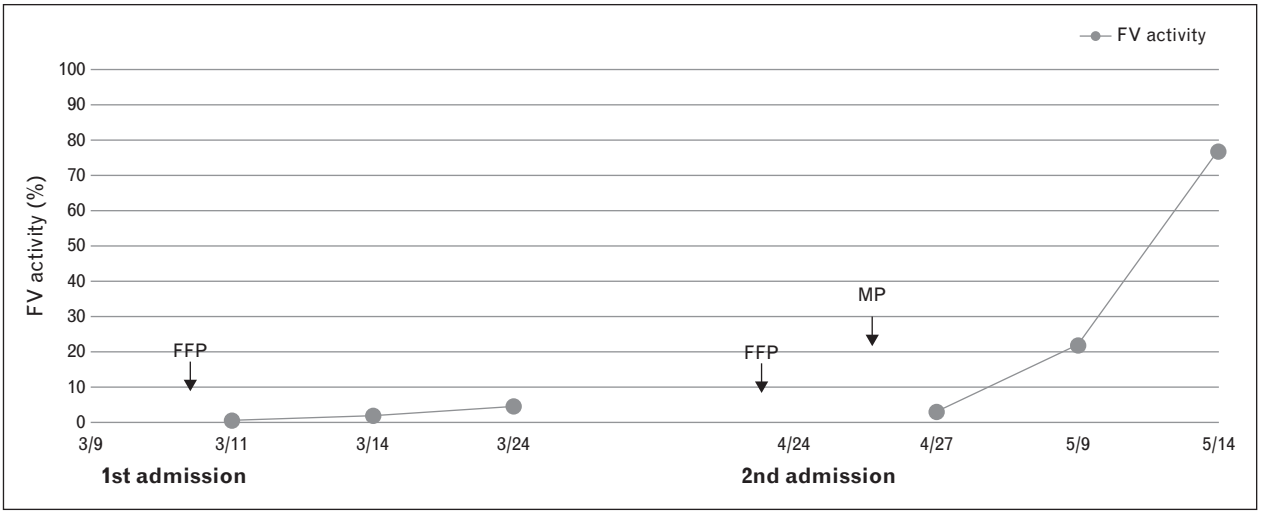


Table 3 Factor V activity results after the first and second admissions

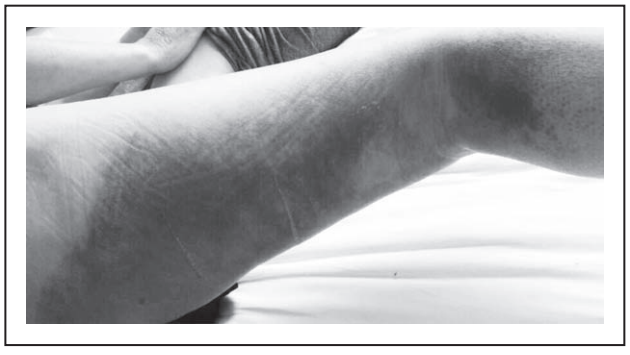


assays of his relatives revealed that his two daughters and his brother and sister also carried this mutation but never exhibited coagulation disorders. Indeed, the c.1538G>A (1628G>A, Arg485Lys) mutation has been proved to be a polymorphism in people that does not influence the factor V procoagulant activity. After congenital factor V deficiency was ruled out, the patient was started on methylprednisolone (60 mg/day). Five days after the initiation of the steroid treatment, the bleeding symptoms were completely resolved, the bruising on the right lower limb disappeared gradually, serial measurements of the PT/APTT levels remained stable within the reference ranges, and the factor V activity increased to normal (77%, Table 3). Further follow-up showed his coagulation parameters (PT/APTT) and factor V activity were normal and no factor V inhibitors were detected (Table 4).

Discussion and literature review

AFVD is a rare haemostatic disorder; the clinical manifestations of which are variable and range from asymptomatic haematological laboratory abnormalities to life-threatening haemorrhaging or thromboembolic events. Acquired factor V inhibitors are rare causes of clinical bleeding with severities that range from mild to life threatening. Notably, multiple bleeding sites are infrequently and simultaneously (32%) involved [3]. Mucous membranes (i.e. the gastrointestinal, genitourinary, and airway tracts) are most frequently involved in the bleeding. The mortality rate of patients with haemorrhages can reach 21% [4]. Thrombotic events are rare. Notably, only six patients on factor V inhibitors have presented with thrombotic manifestations that include limb gangrene [5], multiple cerebral infarctions [6], deep vein thromboli [7–9], and upper extremity thrombi [10].

Fig. 1



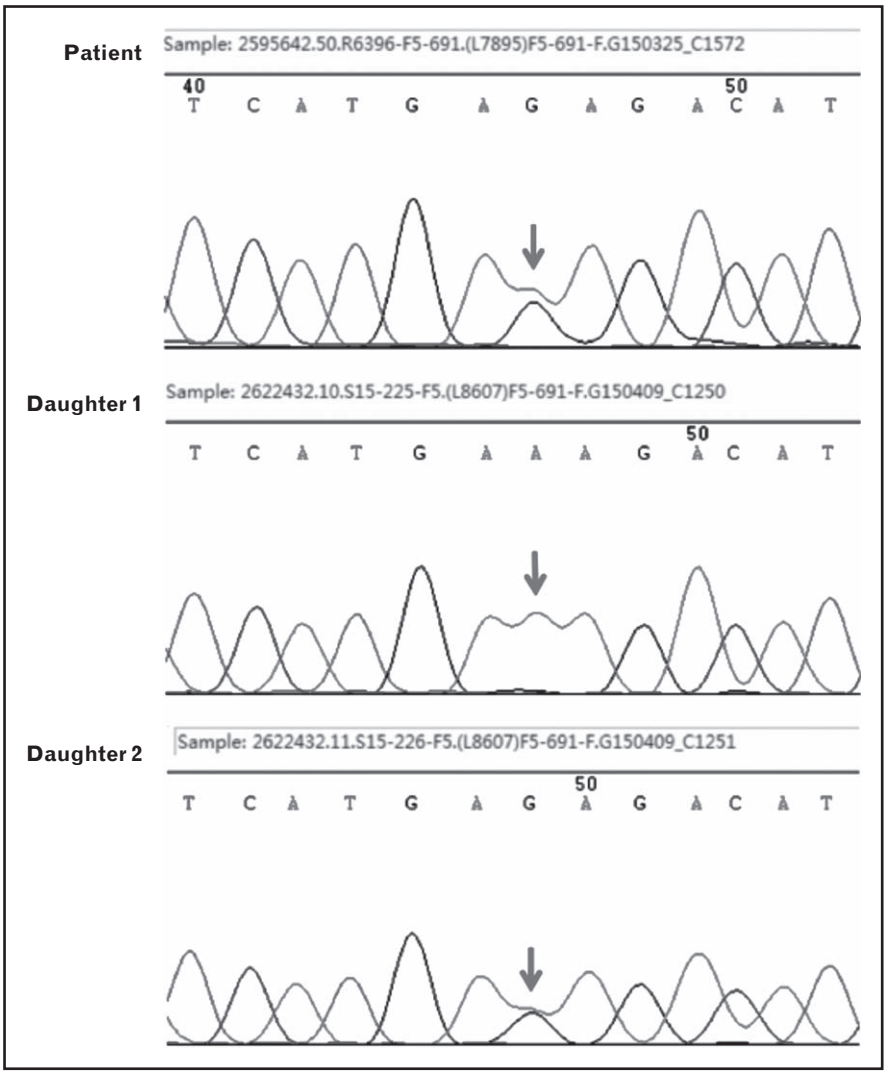
Skin bruising on the right lower limb of the patient.

In the present case, the patient initially presented with haematuria and subsequently developed multiple haemorrhages that included nose bleeding, tonsil bleeding, gingival bleeding, and haematoma. Because multiple haemorrhages are frequently involved in AFVD, we assume that AFVD should be considered for patients who present with bleeding, particularly those who present with multiple haemorrhages.

AFVD is generally because of the development of antibodies against factor V. Regarding the conditions associated with the development of factor V inhibitors, a review of 148 cases of AFVD between 1955 and 2010 in the literature revealed that the majority of these cases were associated with exposure to bovine thrombin during surgical procedures, antibiotics (cephalosporins, aminoglycosides, and penicillins), infections, malignancies, and autoimmune diseases [3]. However, the author noted that it was difficult to prove causation or association in many of these cases.

A PubMed and CNKI search from 2010 to 2016 and a subsequent search from 1955 to 2016 were performed

Fig. 2



The c.1538G>A (1628G>A, Arg485Lys) mutation in the patient and his daughters.

with the limits of only the English and Chinese languages (abstracts and reports in other language were also included as long as they had sufficient interpretable information to fulfil the criteria) using the following terms: 'acquired factor V deficiency', 'acquired factor V inhibitors', 'acquired inhibitors and coagulation factors', 'antifactor V antibodies', 'factor V autoantibodies', 'autoimmune factor V inhibitors', 'spontaneous inhibitors', and 'factor V'.

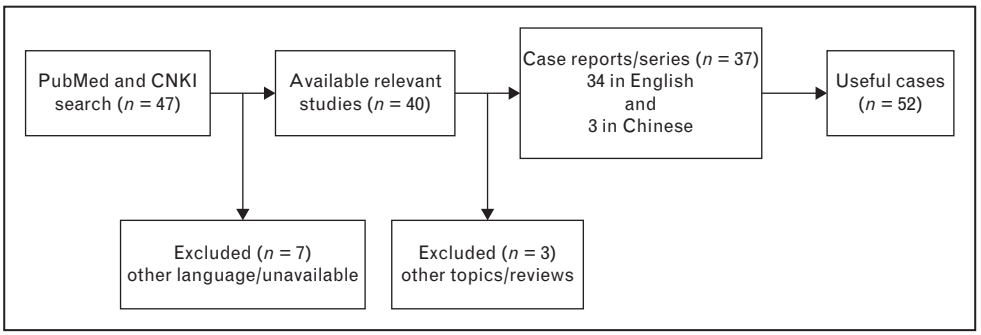
According to the procedure illustrated in Fig. 3, we obtained 34 case reports or series (45 cases) from PubMed and three case reports or series seven cases) from CNKI (Table 5). We reviewed this total of 52 cases of AFVD

Table 4 Follow-up results

Date	2 May 2015	30 July 2015	3 September 2015	10 September 2015	20 September 2015	27 October 2015	11 November 2015	21 January 2016
PT		11.8 s			13.4 s	12.9 s	14.6 s	20.1 s
APTT		23.5 s			37.6 s	28.5 s	31.1 s	52.1 s
FV activity (%)	127	121	73	143				
FV inhibitor	0 BU/ml							

APTT, activated partial thromboplastin time; BU, Bethesda units; FV, factor V; PT, prothrombin time.

Fig. 3



Flow chart of the analysis of the literature.

since 2010 for the underlying conditions of AFVD. Bovine thrombin, which contains only human-derived compounds, was minimally found in the cases; bovine thrombin exposure was only present in four of the 52 cases. In the nonbovine-associated factor V deficiency cases, surgical procedures were present in nine of the 48 nonbovine-associated cases (19%), the use of antibiotics accounted for 19% (9/48), and autoimmune diseases and drugs other than antibiotics both accounted for 9% (4/48). Tumours and other diseases each accounted for 8% (4/48), and infections and transplantations accounted for 13% (6/48) and 4% (2/48), respectively. Interestingly, there were also 13 idiopathic cases (27%, Table 6). We systematically reviewed 200 cases of AFVD from 1955 to 2016 for the underlying conditions of AFVD. Bovine thrombin exposure was present in 74 of the 200 cases. In the nonbovine-associated factor V inhibitor cases, the use of antibiotics was present in 42 of the 126 cases of nonbovine thrombin exposure (33%). Surgical procedures accounted for 26% (33/126), tumours accounted for 17% (21/126), autoimmune diseases accounted for 11% (14/126), infections accounted for 17% (22/126), transplantations accounted for 5% (6/126), and drugs other than antibiotics accounted for 4% (5/126). There were also 29 idiopathic cases (23%, Table 7).

In the present case, the patient had histories of prostatic hyperplasia for 10 years, a surgery, a recent urinary tract infection and the use of antibiotics. The patient had no familial or personal history of coagulopathy. His initial coagulation parameters (PT/APTT) and those during the surgery were normal. Moreover, prior to the initiation of antibiotics, he developed haematuria and multiple haemorrhages. Because hepatitis virus infections and liver dysfunction have been associated with factor V inhibitors [3], the patient's liver function was evaluated to rule out liver disease as a potential cause. However, this patient exhibited no liver dysfunction, liver failure, or hepatitis virus infection as indicate by these laboratory findings (Table 1). Therefore, we assumed the development of the factor V inhibition was associated with a urinary tract infection. Our case is not the only case that has been associated with urinary tract infection. Two other cases involving antibiotics accompanied with urinary tract infections related to conditions of AFVD have been reported [11,12], including one case with a urinary tract infection and the use of ciprofloxacin and an additional case with a urinary tract infection and the use of cephradine. The latter case highlighted that the relationship between the formation of factor V inhibitors and cephradine treatment is probable. Therefore, our case is the first reported AFVD case with a urinary tract infection as the only associated condition. The underlying mechanism might be immunologic dissonance triggered by a urinary tract infection. However, we would like to highlight that it is difficult to be certain that the urinary tract infection played a causative role in this patient in terms of either the development of the inhibitors or the bleeding.

The identification of factor V inhibitors typically occurs in association with prolonged PT and APTT and/or an isolated factor V deficiency in patients with otherwise negative personal and familial haemorrhagic histories. The inhibitor was confirmed and titrated using the traditional Bethesda method. The median peak inhibitor titre was 19 BU (0.5–1500 BU), whereas the median factor V activity level was 1% (1–20%). The inhibitor titre does not correlate with the factor V deficiency level nor with the bleeding risk (the median inhibitor titres in both bleeders and nonbleeders are 19 BU) [3].

In the present case, the factor V inhibitor was initially titrated at 1.9 BU and was subsequently undetectable after the FFP transfusion, which indicates that this was a rare case with an extremely low factor V inhibitor level. The infusion of factor V in FFP was presumed to neutralize some of the inhibitory activity.

Table 5 **Acquired factor V deficiency cases: data in the literature**

No.	Year	Sex	Age	Symptoms at diagnosis	Associated drug/condition	Inhibitor (BU/ml)	FV activity	Treatment	Outcome
1	2010	M	71	Gross haematuria + gastrointestinal bleeding + left groin haematoma	CPS, UTI	6.6	6.2%	Steroids	Death
2	2010	F	88	No	CPS	4	6%	RBC + FFP + rFVIIa + PLT + IVIg + RTX	Inhibitor persistence
3	2010	M	74	Epistaxis	Laparoscopic low anterior resection of rectal cancer[a]	–	–	Plasmapheresis + rFVIIa + PLT	Inhibitor persistence
4	2010	M	3	No	CTS[b]	0–1.0	<6%	IVIg + steroids	Remission
5	2010	F	38	Excessive bleeding	Burn surgery[b]	9	–	FFP	Partially corrected
6	2010	F	84	No	Valve replacement[b] + pyelonephritis + antibiotics + warfarin	8	4%	Steroids	Remission
7	2011	F	28	Gastrointestinal bleeding	LT[a]	10	<1%	FFP + PCC + steroids + IVIg	Inhibitor persistence
8	2011	F	59	Melena	Ovarian tumour	10–18	2.1%	Plasmapheresis	Relapse
9		M	67	No	Antibiotics + UC	3	1.6%	No	Spontaneous resolution
10		M	64	Haematuria + bleeding in soft tissues	None	3	4%	Cyclosporin A	Remission
11	2011	M	88	Microscopic haematuria	Hashimoto's thyroiditis	4.3	1%	Steroids	Remission
12	2011	M	79	POB	Right hip arthroplasty[a]	3	15%	PLT + CTX + steroids	Remission
13	2011	F	80	Gastrointestinal bleeding	None	17	<3%	Steroids	Inhibitor persistence
14	2012	M	85	Chest wall haematoma	Antibiotics	>50	0	Steroids + PLT + IVIg + CTX	Remission
15	2012	M	–	Bleeding	Amiodarone	32.2	3.38%	Steroids + CTX	Remission
16	2012	M	70	Intracerebral haemorrhage	MPA	–	0%	FFP + plasmapheresis	Death
17	2012	F	73	Purpura	None	1.4	2%	Steroids	Inhibitor persistence
18	2012	F	79	Melena + bruises	None	2.0	<1%	FFP + PLT	Lost follow-up
19	2012	M	51	Epistaxis + Haematuria	None	16	1.1%	FFP + steroids + CTX	Remission
20		F	61	Gum bleeds	None	0	0.6%	Steroids	Remission
21		M	71	Melena + bruises	None	3	0.5%	FFP + PCC + steroids + CTX	Death
22	2012	F	72	Haematoma in the oral cavity	None	–	<2%	CTX + RTX	Inhibitor persistence
23		M	51	Haematuria + gum bleeds + epistaxis+ haematomas in upper and lower limbs	None	17	<3%	PLT + steroids + CTX + AZT + RTX	Remission
24	2012	M	8 days	Umbilical bleeding + haematuria	Pneumonia + cefaclor	–	3.6%	RBC + FFP	Remission
25	2012	F	82	DVT	Aspirin, clopidogrel, PCI for UA[a]	4	2%	Steroids	Remission
26	2013	M	85	Skin bleeding	Warfarin	11	<2%	Steroids	Remission
27	2013	M	62	Cerebral haemorrhage + purpura	MN	4.4	2.5%	Steroids	Remission
28	2013	M	82	Epistaxis + Haematuria + Melena	SCC of oesophagus	12	2%	Steroids	Death
29	2014	M	90	Generalized ecchymoses	DEM	4	<3%	Steroids	Inhibitor persistence
30	2014	M	64	Haematuria	MCL	80	<0.01 IU/ml	Steroids	Remission
31	2014	F	64	No	None	–	1%	FFP + steroids + IVIg	Inhibitor persistence
32	2014	M	80	No	Antibiotics	–	–	–	Remission
33	2014	M	–	No	Chronic thyroiditis	4.3	2.3 IU/dl	–	–
34		M	–	No	Progressive supranuclear palsy	5.4	11.5 IU/dl	–	–
35		M	–	No	IPMNs of the pancreas	11.8	<1.0 IU/dl	–	–
36		M	–	No	AF	1.7	<1.0 IU/dl	–	–
37		F	–	No	None	8.7	1.7 IU/dl	–	–
38		M	–	Severe bleeding	AP, asthma	118	8.0 IU/dl	–	–
39		F	–	Severe bleeding	Valve replacement[a]	16	<1.0 IU/dl	–	–
40		M	–	Severe bleeding	CRF	64	<1.0 IU/dl	–	–
41		M	–	Severe bleeding	None	9.9	<1.0 IU/dl	–	–
42		M	–	Severe bleeding	None	8.2	<1.0 IU/dl	–	–
43	2014	F	67	Epistaxis + urethral bleeding + mucosal mouth bleeding	Aortic aneurysm surgery	7.76	5%	FFP + steroids	Remission

Table 5 (*continued*)

No.	Year	Sex	Age	Symptoms at diagnosis	Associated drug/condition	Inhibitor (BU/ml)	FV activity	Treatment	Outcome
44	2014	M	61	Haemoptysis	Lung surgery for empyema[a]	83	<3%	Steroids + RTX	Remission
45	2014	M	54	Gastrointestinal bleeding	LT[a]	9	0.6%	FFP + PLT + PCC + rFVIIa + IVig	Remission
46	2014	M	67	Intra-abdominal bleeding	Hepatectomy for HCC[b]	–	<50%	Steroids	Remission
47	2014	M	82	No	Valve replacement[a]	16	<1%	No	Death
48	2015	M	53	Haematuria	Surgery	6	1%	RTX + IVig + plasmapheresis	Remission
49	2015	M	84	No	Surgery for a ruptured intracerebral haemangioma[a]	212	<5%	PLT + PCC	Death
50	2015	M	59	No	CAZ	10	2%	Steroids	Remission
51	2016	F	64	Upper-extremity thrombus	PTZ, CFX	5	2%,	Steroids	Remission
52		F	75	Minor ecchymosis	PTZ, HCV	21.76	<1%	Steroids	Remission

AF, atrial fibrillation; AFVD, acquired factor V deficiency; AP, aspiration pneumonia; AZT, azathioprine; CAZ, ceftazidime; CFX, ciprofloxacin; CPS, cephalosporin; CRF, Chronic renal failure; CTS, cardiothoracic surgery; CTX, cyclophosphamide; DEM, dabigatran etexilate methanesulfonate; DVT, deep vein thrombosis; F, female; FFP, fresh frozen plasma; FV, factor V; HCC, hepatocellular carcinoma; IPMNs, intraductal papillary-mucinous neoplasms; IVig, intravenous immunoglobulin; LT, liver transplantation; M, male; MCL, mantle cell lymphoma; MN, Membranous nephropathy; MPA, microscopic polyangiitis; ND, no data; PCC, prothrombin complex concentrates; PCI, percutaneous coronary intervention; PLT, platelet; POB, postoperative bleeding; PTZ, piperacillin–tazobactam; RBC, red blood cell; rFVIIa, recombinant-activated factor VII; RTX, rituximab; SCC, squamous cell carcinoma; UA, unstable angina; UC, ulcerative colitis; UTI, urinary tract infection. Not available. [a]No bovine thrombin exposure. [b]Bovine thrombin exposure.

Table 6 **Acquired factor V deficiency cases from 2010 to 2016**

Conditions associated with factor V inhibitors	
Bovine thrombin	$n = 4$
Not bovine thrombin	$n = 48$
Antibiotics	$n = 9$, 19%
Surgery	$n = 9$, 19%
Tumour	$n = 4$, 8%
Autoimmune disease	$n = 4$, 8%
Infection	$n = 6$, 13%
Transplantation	$n = 2$, 4%
Other drugs	$n = 5$, 10%
Other diseases	$n = 4$, 8%
Idiopathic	$n = 13$, 27%
	(Proportion of not bovine thrombin)

Factor V deficiency can be inherited or acquired

Congenital factor V deficiency is an autosomal recessive disease with a prevalence of approximately 1/1 000 000. The mechanism underlying this disorder may involve genetic changes that affect the protein C anticoagulant system, such as the APC caused by a factor V Leiden mutation, deficiencies of protein C, protein S or antithrombin, and increased levels of factor VIII or prothrombin [13]. In terms of treating congenital factor V deficiency, FFP transfusion can easily correct this disorder.

In the present case, evaluations for congenital factor V deficiency did not reveal any possible underlying reason with the exception of the c.1538G>A (1628G>A, Arg485Lys) mutation. The 1628G>A mutation at exon 10 of the factor V gene was first described by Gandrille *et al.* [14]. A G>A transition occurred at nucleotide 1628 in the codon AGA of Arg 485, which was replaced by an AAA codon, which predicted a Lys residue. According to Gandrille, this Lys substitution that occurred at Arg 485 did not influence the APC resistance test nor the factor V procoagulant activity; thus, this substitution is a polymorphism.

Regarding AFVD treatment, it includes bleeding control and the elimination of the factor V inhibitor. FFP, platelet transfusions, and prothrombin complex concentrates have been used in bleeding patients, but the effects of these treatments have mostly been dismal because of the low concentration of factor V. Platelet concentrates

Table 7 **Acquired factor V deficiency cases from 1955 to 2016**

Conditions associated with factor V inhibitors	
Bovine thrombin	$n = 74$
Not bovine thrombin	$n = 126$
Antibiotics	$n = 42$, 33%
Surgery	$n = 33$, 26%
Tumour	$n = 21$, 17%
Autoimmune disease	$n = 14$, 11%
Infection	$n = 21$, 17%
Transplantation	$n = 6$, 5%
Other drugs	$n = 5$, 4%
Idiopathic	$n = 29$, 23%
	(Proportion of not bovine thrombin)

Table 8 Treatments for acquired factor V deficiency

Bleeding control
Fresh frozen plasma
Platelet transfusion
Prothrombin complex concentrates
Recombinant-activated factor VII
Eradication of the autoantibody
Corticosteroids
Cyclophosphamide
Rituximab
Intravenous immunoglobulin
Plasmapheresis and immunoadsorption

can protect factor V from inhibitors thus produce a satisfactory effect in terms of bleeding control. Recombinant-activated factor VII acts as a bypassing agent and has also been successfully used in factor V deficiency cases with severe haemorrhaging. The other principle for managing patients with factor V inhibitors has been the eradication of these inhibitors, and the gold standard has been immunosuppression (i.e. corticosteroids, cyclophosphamide, and rituximab). Corticosteroids can eradicate factor V inhibitors to reduce subsequent bleeding risk because of their immunosuppressive effects. Specifically, immunosuppressive regimens with corticosteroids alone or in association with cyclophosphamide or other immunosuppressants were successfully used to suppress autoantibody production in 76 of 126 cases (60%), and remissions were achieved in 37 of these cases (29%). High intravenous doses of immunoglobulin can rapidly increase factor V activity by reducing factor V inhibitors. Extracorporeal methods, such as plasmapheresis and immunoadsorption, can also reduce factor V inhibitors and thus effectively control bleeding (Table 8).

In the present case, the PT/APTT decreased following each FFP transfusion but subsequently increased over the following days, which suggests the reequilibration of the inhibitor from the extravascular fluid and the continued production of the inhibitor. After a 5-day course of high-dose corticosteroids, the PT/APTT and factor V activity were both corrected to normal. We assumed that immunosuppressive regimens of corticosteroids can eliminate factor V inhibitors and thus effectively increase the factor V activity and control bleeding.

Conclusion

This is the first reported case of AFVD that is possibly associated only with a urinary tract infection. The clinical and laboratory features and treatment of this disease were discussed. Additionally, we systematically reviewed 200 cases of AFVD from 1955 to 2016 for the conditions underlying AFVD.

Acquired inhibitors of factor V are rare causes of clinical bleeding, and multiple haemorrhages are not rare. Therefore, we assume that AFVD should be kept in mind for patients who present with bleeding, especially those who present with multiple haemorrhages, and immediate treatment should be administered because the condition may cause life-threatening complications.

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Conflicts of interest

There are no conflicts of interest.

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