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 Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.

Keywords: acquired factor V deficiency, corticosteroids, factor V inhibitors, haemorrhage, urinary tract infection

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Received 2 January 2016 Revised 15 May 2016 Accepted 21 May 2016

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 procoagulation 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 × 10⁹/l (3.8–5.1 × 10⁹/l), his white blood cell count was 7.9 × 10⁹/l (3.5–9.5 × 10⁹/l), his...
The platelet count was 162 $/\times 10^9$ (125–350 $/\times 10^9$), 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 $/\times 10^9$ and 144 $/\times 10^9$ 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 $\rightarrow$ A (1628G $\rightarrow$ A, Arg485Lys) mutation was detected (Fig. 2). However, screening

**Table 1 Laboratory findings**

| Blood chemistry | ALT (IU/l) | AST (IU/l) | GGT (IU/l) | AKP (IU/l) | LDH (IU/l) | TP (g/l) | ALB (g/l) | TBIL (µmol/l) | DBIL (µmol/l) | IBIL (µmol/l) | Cr (µmol/l) | Na (mmol/l) |
|----------------|-----------|-----------|-----------|------------|-----------|---------|---------|------------|-------------|-------------|----------|-----------|
| K              | 3.78 (3.50–5.30) | 1103 (99–110) |          | 90 (45–125) | 270 (120–230) |         | 48.2 (40.0–55.0) | 5.3 (5.0–21.0) | 2.1 (0.0–6.0) | 1.0 (0.0–6.0) | 3.2 (2.0–15.0) | 5.68 (2.30–7.80) |
| Cytology       | ALT       | AST       | GGT       | AKP        | LDH       | TP       | ALB      | TBIL       | DBIL       | IBIL       | Cr        | Na        |
|                | 17        | 15        | 31        | 90         | 270       | 73.2    | 48.2     | 5.3        | 2.1        | 3.2        | 65       | 142       |
|                | (9–50)    | (15–40)   | (10–60)   | (45–125)   | (120–230) | (6.0–85.0) | (40.0–55.0) | (5.0–21.0) | (0.0–6.0) | (2.0–15.0) | (262–115) | (137–147) |

AKP, alkaline phosphatase; ALB, albumin; ALT, alanineaminotransferase; AST, aspartate transferase; 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, antibody to hepatitis B e-antigen; HBeAb, antibody to hepatitis B e-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; SERPINC1, serpin C1; TP, total protein; TP-Ab, treponema pallidum antibody; –, negative.

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

| MP | PT | APTT |
|----|----|------|
| FFP| FFP| FFP  |
| 3/8| 3/11| 3/14 |
| 3/13| 3/16| 3/19 |
| 3/21| 3/26| 3/30 |
| 4/2| 4/23| 4/25 |
| 4/27| 4/30| 5/3 |
| 5/6| 5/9| 5/11 |
| 5/14| | |
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].

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...
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.
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 | | 4 | 6% | RBC + FFP + rFVIIa + PLT + IVIg + RTX Inhibitor persistence |
| 3   | 2010 | M   | 74  | Epistaxis | Laparoscopic low anterior resection of rectal cancera | – | – | Plasmapheresis + rFVIIa + PLT | Inhibitor persistence |
| 4   | 2010 | M   | 3   | No | CTPs | 0–1.0 | <6% | IVIg + steroids | Remission |
| 5   | 2010 | F   | 38  | Excessive bleeding | Bum surgeryb | 9 | – | FFP | Partially corrected |
| 6   | 2010 | F   | 84  | No | Valve replacement + peyelophraxis + antibiotics + warfarin | 8 | 4% | Steroids | Remission |
| 7   | 2011 | F   | 28  | Gastrointestinal bleeding | LT | 10 | <1% | FFP + PCC + steroids + IVIg | Inhibitor persistence |
| 8   | 2011 | F   | 59  | Melena | Ovarian tumour | 10–18 | 2.1% | Plasmapheresis | Remission |
| 9   | 2011 | M   | 67  | No | Antibiotics + UC | 3 | 1.6% | No | Spontaneous resolution |
| 10  | 2011 | 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 | F   | 79  | POB | Right hip arthroplastyb | 3 | 15% | PLT + CTX + steroids | Remission |
| 13  | 2011 | F   | 80  | Gastrointestinal bleeding | None | 17 | <3% | Steroids | Inhibitor persistence |
| 14  | 2012 | M   | 85  | Chest wall haematuria | 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 | 14 | 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  | 2012 | F   | 61  | Gum bleeds | None | 0 | 0.8% | Steroids | Remission |
| 21  | 2012 | M   | 71  | Melena + bruises | None | 3 | 0.5% | FFP + PCC + steroids + CTX | Death |
| 22  | 2012 | F   | 72  | Haematuria in the oral cavity | None | – | <2% | CTX + RTX | Inhibitor persistence |
| 23  | 2012 | 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 + cefalex | – | 3.6% | RBC + FFP | Remission |
| 25  | 2012 | F   | 82  | DVT | Aspirin, clopidogrel, PCI for UAa | 4 | 2% | Steroids | Remission |
| 26  | 2013 | M   | 85  | Skin bleeding | Warfarin | 11 | <2% | Steroids | Remission |
| 27  | 2013 | M   | 62  | Cerebral haemorrhage + purpura | MN | 44 | 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 | – | – | – | – |
| 33  | 2014 | M   | –   | No | Chronic thyroiditis | 4.3 | 2.3 IU/dl | – | – |
| 34  | 2014 | M   | –   | No | Progressive supranuclear palsy | 5.4 | 11.5 IU/dl | – | – |
| 35  | 2014 | M   | –   | No | IPMN of the pancreas | 11.8 | <1.0 IU/dl | – | – |
| 36  | 2014 | M   | –   | No | AF | 1.7 | <1.0 IU/dl | – | – |
| 37  | 2014 | F   | –   | No | None | 8.7 | 1.7 IU/dl | – | – |
| 38  | 2014 | M   | –   | Severe bleeding | AP, asthma | 118 | 8.0 IU/dl | – | – |
| 39  | 2014 | F   | –   | Severe bleeding | Valve replacementb | 16 | <1.0 IU/dl | – | – |
| 40  | 2014 | M   | –   | Severe bleeding | CRF | 64 | <1.0 IU/dl | – | – |
| 41  | 2014 | M   | –   | Severe bleeding | None | 91 | <1.0 IU/dl | – | – |
| 42  | 2014 | M   | –   | Severe bleeding | None | 82 | <1.0 IU/dl | – | – |
| 43  | 2014 | F   | 67  | Epistaxis + urethral bleeding + mucosal mouth bleeding | Aortic aneurysm surgery | 7.76 | 5% | FFP + steroids | Remission |
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 6

| Year | Sex | Age | Symptoms at diagnosis | Associated drug/condition | Inhibitor (BU/ml) | FV activity | Treatment | Outcome |
|------|-----|-----|-----------------------|---------------------------|-------------------|-------------|-----------|---------|
| 2014 | M   | 61  | Haemoptysis           | Lung surgery for empyema  | -                 | >3%         | FFP, PLT   | Remission|
| 2014 | M   | 69  | Intra-abdominal bleeding | Hepatectomy for HCC      | 16                | >1%         | PLT, PCC   | Remission|
| 2015 | M   | 84  | No                    | RBC not blood cell, g7G   | 212               | >2%         | rFVIIa, IVIg | Remission|
| 2015 | M   | 84  | No                    | No                          | 83                | >3%         | Remission |
| 2016 | M   | 88  | No                    | No                          | 64                | >2%         | Remission |
| 2016 | F   | 66  | No                    | No                          | 84                | >2%         | Remission |

AF, atrial fibrillation; AD, acquired factor V deficiency; AG, agglutination; AL, allergic; AS, aspirin; AT, aspergillus; CAZ, ciprofloxacin; CBS, cephalosporin; CMS, cephalosporin; CRS, chronic renal failure; CTS, cardiothoracic surgery; CX, chest x-ray; 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; g7G, g7G, g7G, g7G; UI, uri, urin, urin, urin; UUI, uri, uri, uri, uri, uri; UC, uro, uro, uro, uro, uro, uro, uro.

### Table 7

| Year | Sex | Age | Symptoms at diagnosis | Associated drug/condition | Inhibitor (BU/ml) | FV activity | Treatment | Outcome |
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| 2015 | M   | 84  | No                    | No                          | 83                | >3%         | Remission |
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### Factor V deficiency can be inherited or acquired

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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
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.

**Acknowledgements**

There are no conflicts of interest.

**References**

1. Ang AL, Kuperan P, Ng CH, Ng HJ. Acquired factor V inhibitor. A problem-based systematic review. *Thromb Haemost* 2009; 101:852–859.
2. Favaloro EJ, Posen J, Ramakrishna R, Soltani S, McRae S, Just S, et al. Factor V inhibitors: rare or not so uncommon? A multilaboratory investigation. *Blood Coagul Fibrinolysis* 2004; 15:637–647.
3. Franchini M, Lippi G. Acquired factor V inhibitors: a systematic review. *J Thromb Thrombolysis* 2011; 31:449–457.
4. William BM. Adjunctive role for recombinant activated factor VII in the treatment of bleeding secondary to a factor V inhibitor. *Blood Coagul Fibrinolysis* 2006; 19:327–328.
5. Kapur A, Kelsey PR, Isaacs PE. Factor V inhibitor in thrombosis. *Am J Hematol* 1993: 42:384–388.
6. Koyama T, Saito T, Kusano T, Hiroswa S. Factor V inhibitor associated with Sjogren’s syndrome. *Br J Haematol* 1995; 99:893–896.
7. Kamphuisen PW, Haan J, Rosekrans PC, Van Der Meer FJ. Deep-vein thrombosis and coumarin skin necrosis associated with a factor V inhibitor with lupus-like features. *Am J Hematol* 1998; 57:176–178.
8. Kalafatis M, Simioni P, Tormene D, Beck GO, 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* 2002; 99:3985–3992.
9. Higuchi T, Okamoto T, Kau T, Takeuchi T, Koyamada R, Okada S. Deep vein thrombosis associated with factor V inhibitor followed by immune thrombocytopenia. *Ann Hematol* 2012; 91:1831–1832.
10. Gavva C, Yates SG, Rambally S, Sarode R. Transfusion management of factor V deficiency: three case reports and review of the literature. *Transfusion* 2016; doi: 10.1111/trf.13823. PubMed PMID: 27125565.
11. Fu YX, Kaufman R, Rudolph AE, Collum SE, Blinder MA. Multimodality therapy of an acquired factor V inhibitor. *Am J Hematol* 1996; 51:315–319.
12. Wu MT, Pei SN. Development of cephradine-induced acquired factor V inhibitors: a case report. *Ann Pharmacother* 2010; 44:1673–1676.
13. Segers K, Dahlback B, Nicolaas GA. Coagulation factor V and thrombophilia: background and mechanisms. *Thromb Haemost* 2007; 98:530–542.
14. Gandrille S, Greengard JS, Alhenc-Gelas M, Johan-Vague I, Abgrall JF, Jude B, et al. Incidence of activated protein C resistance caused by the ARG 506 GLN mutation in factor V in 113 unrelated symptomatic protein C-deficient patients. The French Network on the behalf of INSERM. *Blood* 1995; 86:219–224.

**Table 8  Treatments for acquired factor V deficiency**

| Treatment                          |
|-----------------------------------|
| **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 |

**References**

1. Ang AL, Kuperan P, Ng CH, Ng HJ. Acquired factor V inhibitor. A problem-based systematic review. *Thromb Haemost* 2009; 101:852–859.
2. Favaloro EJ, Posen J, Ramakrishna R, Soltani S, McRae S, Just S, et al. Factor V inhibitors: rare or not so uncommon? A multilaboratory investigation. *Blood Coagul Fibrinolysis* 2004; 15:637–647.
3. Franchini M, Lippi G. Acquired factor V inhibitors: a systematic review. *J Thromb Thrombolysis* 2011; 31:449–457.
4. William BM. Adjunctive role for recombinant activated factor VII in the treatment of bleeding secondary to a factor V inhibitor. *Blood Coagul Fibrinolysis* 2006; 19:327–328.
5. Kapur A, Kelsey PR, Isaacs PE. Factor V inhibitor in thrombosis. *Am J Hematol* 1993; 42:384–388.
6. Koyama T, Saito T, Kusano T, Hiroswa S. Factor V inhibitor associated with Sjogren’s syndrome. *Br J Haematol* 1995; 99:893–896.
7. Kamphuisen PW, Haan J, Rosekrans PC, Van Der Meer FJ. Deep-vein thrombosis and coumarin skin necrosis associated with a factor V inhibitor with lupus-like features. *Am J Hematol* 1998; 57:176–178.
8. Kalafatis M, Simioni P, Tormene D, Beck GO, 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* 2002; 99:3985–3992.
9. Higuchi T, Okamoto T, Kau T, Takeuchi T, Koyamada R, Okada S. Deep vein thrombosis associated with factor V inhibitor followed by immune thrombocytopenia. *Ann Hematol* 2012; 91:1831–1832.
10. Gavva C, Yates SG, Rambally S, Sarode R. Transfusion management of factor V deficiency: three case reports and review of the literature. *Transfusion* 2016; doi: 10.1111/trf.13823. PubMed PMID: 27125565.
11. Fu YX, Kaufman R, Rudolph AE, Collum SE, Blinder MA. Multimodality therapy of an acquired factor V inhibitor. *Am J Hematol* 1996; 51:315–319.
12. Wu MT, Pei SN. Development of cephradine-induced acquired factor V inhibitors: a case report. *Ann Pharmacother* 2010; 44:1673–1676.
13. Segers K, Dahlback B, Nicolaas GA. Coagulation factor V and thrombophilia: background and mechanisms. *Thromb Haemost* 2007; 98:530–542.
14. Gandrille S, Greengard JS, Alhenc-Gelas M, Johan-Vague I, Abgrall JF, Jude B, et al. Incidence of activated protein C resistance caused by the ARG 506 GLN mutation in factor V in 113 unrelated symptomatic protein C-deficient patients. The French Network on the behalf of INSERM. *Blood* 1995; 86:219–224.