Transfusion management of Factor V deficiency: three case reports and review of the literature

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BACKGROUND: Factor V (FV) deficiency may be inherited as an autosomal recessive disease or acquired as a result of autoantibody formation, either spontaneously or secondary to exposure to bovine thrombin or medications. Congenital FV deficiency has traditionally been treated with plasma transfusions. However, recent evidence has suggested that platelet (PLT) transfusions may be a better alternative as FV stored within PLT alpha granules has greater procoagulant potential and is released locally at sites of vascular injury. We report three cases of FV deficiency, one congenital and two acquired, and emphasize the different management approaches.

CASE REPORTS: Patient 1 was a 30-year-old man with congenital FV deficiency who presented with a trauma-induced hematoma of his lower extremity. He was treated with 5 PLT units over 48 hours. Patient 2 was a 64-year-old woman who presented with an upper-extremity thrombus and was discovered to have a FV inhibitor, likely secondary to antibiotics. Patient 3 was a 75-year-old woman with hepatitis C virus (HCV) who presented with minor ecchymosis and was found to have a FV inhibitor secondary to either HCV or antibiotic exposure. Corticosteroids alone were able to eradicate the inhibitors in both patients with acquired inhibitors.

CONCLUSIONS: FV deficiency can present with a diverse range of symptoms. For bleeding patients, PLT transfusions should be the initial therapy. In patients with thrombosis, the risks and benefits of anticoagulation must be carefully assessed before treatment. For patients with minor bleeds, transfusions may be withheld, and elimination of the inhibitor should be the primary objective.

Factor V (FV) plays an essential role in hemostasis, contributing to both pro- and anticoagulation pathways.[1] It is synthesized primarily by the liver and predominantly circulates in the plasma in its inactive form before undergoing activation by either thrombin or activated Factor X (FXa).[2] However, approximately 25% of FV is stored within platelet (PLT) alpha granules, originating from megakaryocytic endocytosis of plasma FV.[3] Activated FV (FVa) serves as a cofactor for FXa in the prothrombinase complex to convert prothrombin into thrombin on phospholipid surfaces (e.g., PLTs).[2] Activated protein C (APC) inactivates the procoagulant activity of FVa, while intact FV serves as a cofactor (along with protein S) in the APC-facilitated inactivation of activated FVIII.[2]

Congenital FV deficiency is a rare autosomal recessive disorder with an estimated frequency of one in 1,000,000 people.[1] A quantitative reduction in FV protein expression (Type I) is observed in 75% of inherited deficiencies with the remaining recognized as qualitative defects of the protein (Type II).[4] Patients may also suffer from a rare combined FV and FVIII deficiency (F5F8D) as a consequence of defects in the secretory pathways of the two factors.[4]

ABBREVIATIONS: APC = activated protein C; aPCC = activated prothrombin complex concentrate; FXa = activated Factor X; OSH = outside hospital; PT = prothrombin time; PTT = partial thromboplastin time; RUE = right upper extremity; rVIIa = activated recombinant FVII.

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Although plasma transfusions have historically been used to treat congenital FV deficiency, recent evidence suggests that PLT transfusions may be a better alternative as the FV stored in the PLT alpha granules can be delivered locally to the site of injury and carries a greater procoagulant activity.[3]

In addition to inherited deficiencies, approximately 150 cases of acquired FV inhibitors have been reported[2] with the most common association being exposure to bovine thrombin used for topical hemostasis during surgery.[5] Antibodies directed against residual bovine FV found in bovine thrombin products may cross-react and inhibit the patient's own FV.[5] With recombinant thrombin use as well as improved purification methods of bovine thrombin, the risk of developing FV autoantibodies appears to be reduced.[6] Development of FV inhibitors has also been associated with a number of clinical conditions including autoimmune disorders, human immunodeficiency virus, bacterial infections, malignancy, and medications such as beta-lactam or aminoglycoside antibiotics.[5]

Herein, we report one case of congenital and two cases of acquired FV deficiency. These cases highlight the different etiologies of FV deficiency, the variable clinical presentations, diagnostic considerations, and management strategies.

CASE REPORTS

Patient 1

A 30-year-old man with a history of congenital FV deficiency presented to our institution with an enlarging hematoma of his right lower extremity after a large object struck his leg. He attempted to treat his injury with ice packs, elevation, and rest as he generally does for minor soft tissue injuries; however, his hematoma continued to expand.

He was initially diagnosed with congenital FV deficiency as an infant after increased bleeding after circumcision. In childhood, he suffered from frequent episodes of epistaxis, requiring both therapeutic and prophylactic plasma transfusions. As he grew older, he experienced fewer bleeding episodes with his last plasma transfusion being 2 years previously.

Admission prothrombin time (PT), partial thromboplastin time (PTT), and fibrinogen were 38.4 seconds (reference range, 9.5-12.8 sec), 75.5 seconds (reference range, 23.0-32.5 sec), and 361 mg/dL (reference range, 214-459 mg/dL), respectively, while FV activity was 1% (reference range, 88%-135%). PLT count was 226×10^9/L (reference range, $150 \times 10^9 - 450 \times 10^9$/L), and FVIII activity was 155% (reference range, 50%-150%). As this was his first presentation to our hospital, a mixing study was performed, demonstrating complete correction of the PTT both immediately and after 2 hours of incubation at 37°C, ruling out an inhibitor. He was transfused with 1 unit of PLTs every 12 hours. After the first unit, he demonstrated improvement in pain, range of motion, and control of the hematoma. After receiving 2 units of PLTs, his FV activity improved to 8% (mostly due to the plasma present in PLT units), while his PT and PTT shortened to 18.6 and 36.2 seconds, respectively. He was discharged after receiving 5 units of PLTs over 48 hours.

Patient 2

A 64-year-old Hispanic woman with a history of end-stage renal disease (ESRD) secondary to hypertension was admitted with volume overload and pneumonia. She was treated with dialysis, 1 day of azithromycin, and 8 days of piperacillin-tazobactam and vancomycin. Shortly after admission, she began to complain of right upper extremity (RUE) pain. Ultrasound for a venous thrombosis was negative, and she was discharged with 6 days of moxifloxacin.

The patient returned with an exacerbation of volume overload 5 days later. After laboratory studies revealed an elevated white blood cell count of 14.42×10^9/L (reference range, $3.9 \times 10^9 - 10.7 \times 10^9$/L), blood cultures were collected. PT (10.4 sec) and PTT (23.6 sec) were unremarkable. The patient was discharged after dialysis.

One day after discharge, peripheral blood cultures grew Gram-negative rods, and the patient was asked to return to the emergency department. She was treated with 3 days of piperacillin-tazobactam and later switched to ceftriaxone after blood cultures speciated *Enterobacter cloacae*. PT and PTT were again within normal limits. She continued to have RUE pain though repeat ultrasound remained negative for thrombosis. She was discharged with 2 weeks of ciprofloxacin.

Fourteen days later, she returned to the hospital for dialysis with persistent RUE pain. Ultrasound imaging identified an unprovoked partially occlusive thrombus of the right brachiocephalic vein not associated with a peripheral venous catheter. Coagulation tests revealed a markedly prolonged PT of 43.5 seconds and PTT of 70.3 seconds as well as an elevated fibrinogen (530 mg/dL). She denied any recent bleeding, bruising, or petechiae. FII and FX were normal at 75% (reference range, 77%-128%) and 76% (reference range, 82%-144%) respectively. FV activity was decreased at 2%, and a mixing study did not demonstrate correction of PT or PTT immediately or after incubation for 2 hours at 37°C. These findings suggested an inhibitor, which was later confirmed by a Bethesda assay (FV inhibitor of 5 Bethesda units/mL).

She was started on 1 mg/kg prednisone to treat the FV inhibitor. Although her PT and PTT remained prolonged (40.0 and 64.6 sec, respectively), she was discharged with daily prednisone (1 mg/kg). She was managed only with clinical and ultrasound surveillance as her thrombus was in the distal RUE and her risk of bleeding outweighed the

benefits of anticoagulation. When she presented for dialysis 19 days later, her PT (10.2 sec) and PTT (21.9 sec) were normal, and FV activity was slightly elevated at 148%. Prednisone was eventually tapered and discontinued, and 4 months later, her PT and PTT remained within the reference ranges. A repeat ultrasound indicated resolution of the venous thromboembolism.

Patient 3

A 75-year-old woman with a 41-year history of untreated hepatitis C virus and Stage III chronic kidney disease secondary to hypertension presented to an outside hospital (OSH) with progressive shortness of breath. On presentation, her PT was slightly elevated at 15.4 seconds. Due to her progressive decline in renal function, hemodialysis was initiated. Concern for pneumonia led to treatment with vancomycin and piperacillin-tazobactam. Nine days after her presentation, coagulation variables were reassessed before an anticipated kidney biopsy. Her repeat PT and PTT were significantly prolonged (78 and 67.8 sec, respectively). At the OSH, FV activity was less than 6% (reference range, 60%-140%) whereas FVII, FVIII, and FX were 74, 116, and 52%, respectively (reference range 50-150%). Kidney biopsy was postponed due to her coagulopathy, and the patient was transferred to our institution for further workup.

On arrival, physical examination revealed minor bilateral lower extremity ecchymosis in various stages of healing. We confirmed her FV deficiency (activity $< 1\%$) and did not perform other factors assays since they were found to be normal at the OSH. A PT mixing study failed to correct both immediately or after incubation for 2 hours at 37°C, and a Bethesda assay demonstrated a FV inhibitor titer of 21.76 Bethesda units/mL. Daily prednisone (1 mg/kg) was initiated with progressive improvement in her coagulation variables. After normalization of her PT to 13.4 seconds 22 days later, she underwent a kidney biopsy which revealed hepatitis C–associated membranoproliferative glomerulonephritis. One month later, FV activity was 169% with resolution of her ecchymosis, but her renal function had progressed to chronic kidney disease Stage V. Prednisone was discontinued, and long-term dialysis was planned.

DISCUSSION

We described three different presentations of FV deficiency. The congenital FV deficiency patient had gradual improvement in his bleeding tendency since early childhood and responded well to PLT transfusions. The second patient had an acquired FV deficiency due to an autoantibody most likely secondary to antibiotic exposure; however, she presented with thrombosis rather than bleeding. The third case of acquired FV deficiency was most likely secondary to hepatitis C infection or piperacillin-tazobactam exposure with a bleeding tendency that responded well to glucocorticoid therapy without FV supplementation.

Clinical presentation

It is difficult to predict the risk of bleeding based on FV activity alone.[4] Congenital FV-deficient patients with an activity of less than 10% may experience a wide range of symptoms ranging from epistaxis or oral cavity mucosal bleeding to more severe hemorrhagic manifestations including hemarthroses, soft tissue hematomas, menorrhagia, or central nervous system bleeds.[4] This variability in presentation may be due to reduced levels of free tissue factor pathway inhibitor observed in patients with severe FV deficiency.[7] Lower levels of tissue factor pathway inhibitor may serve to balance decreased FV concentrations and promote a milder bleeding tendency. It is also possible that despite having an undetectable plasma FV level, patients with only minor bleeding may still possess residual FV within their PLTs.[8] Reduced FV cofactor activity for APC may also contribute to less significant symptoms in some patients. Those with an activity of more than 15% frequently remain asymptomatic or present with mild bleeding only identified after preoperative PT and PTT testing.[1] Our first patient with a FV activity of 1% experienced only epistaxis, bleeding after circumcision, and posttraumatic bleeding during childhood. Interestingly, his bleeding diathesis seems to have improved as he grew older, reflecting a possible compensatory increase in other coagulation factors including fibrinogen, FVII, FVIII, and FIX.[9]

Patients 2 and 3 both developed a FV autoantibody without exposure to bovine thrombin. Patient 2 was found to have a FV inhibitor after recent treatment with piperacillin-tazobactam and ciprofloxacin while Patient 3 had a history of HCV and formed an inhibitor after recent exposure to piperacillin-tazobactam. HCV, piperacillin-tazobactam, and ciprofloxacin have all been associated with FV inhibitors.[5]

Clinical manifestations of acquired FV deficiency are heterogeneous and may vary from an incidental finding to significant bleeding.[2] Up to 61% of patients present with bleeding at the time of diagnosis with cerebral hemorrhage associated with the highest mortality.[10] In a systematic review of patients with non–bovine-associated FV autoantibodies, it was demonstrated that bleeding patients and asymptomatic patients had median 1 and 3% FV levels, respectively.[5] Furthermore, autoantibodies that are able to inhibit FV stored in PLTs through the endocytosis of immunoglobulins or recognize the C2 domain of FV (essential for binding to PLT surface phospholipids) are more likely to result in bleeding.[5]

Interestingly, our second patient presented with a venous thromboembolism at diagnosis (Patient 2). FV

inhibitors associated with thrombosis have been documented in four previous case reports.[5] It has been speculated that these antibodies may disrupt the interaction between FVa and phospholipid membranes, resulting in diminished inactivation of FVa by APC as well as prolongation of PT and PTT.[11] The antibody may have also prevented FV from serving as a cofactor in the APC-mediated inactivation of activated FVIII, contributing to a prothrombotic state. Additional studies are required to elucidate why some patients with a FV autoantibody present with thrombosis.

Diagnosis

After ruling out common causes of a combined prolonged PT and PTT including disseminated intravascular coagulation and chronic liver disease, we advocate performing specific factor activity assays (FII, FV, and FX) to identify the deficient coagulation factor. Mixing studies are not standardized across laboratories and consequently may result in false-negative results in the presence of a weak inhibitor.[12] They are also time- and labor-intensive, factors that may significantly delay a diagnosis. Once a specific factor activity assay identifies a factor deficiency (in this case FV), a mixing study may be conducted to detect the presence of an autoantibody or help ensure that a patient with a congenital deficiency has not subsequently developed alloantibodies due to previous plasma transfusions. FV inhibitors are usually immediate acting; however, a few case reports have demonstrated time and temperature dependency.[13] A traditional Bethesda assay can be used to measure inhibitor strength.[10] We also recommend obtaining a FVIII activity level in patients with a congenital deficiency to ensure that there is not a combined deficiency.[14]

Treatment

Historically, plasma has been advocated as the treatment of choice for bleeding patients with a congenital FV deficiency.[4] Depending on the severity of bleeding, this may require a loading dose of 20 mL/kg of plasma followed by 5 mL/kg every 12 hours,[15] placing the patient at risk of volume overload, transfusion-transmitted diseases, and severe allergic reactions.[16]

Alternatively, we recommend PLT transfusions as the first-line therapy for bleeding due to a congenital or acquired FV deficiency. PLTs localize at the site of vascular injury, releasing high concentrations of FV from alpha granules that promote thrombin generation on PLT surfaces.[3,4] Furthermore, FV stored within PLTs has been shown to carry a greater procoagulant potential relative to circulating FV in plasma, likely attributable to intracellular modifications within PLTs.[3] The use of PLTs also confers a few practical advantages compared to plasma including reduced donor exposure, decreased risk of allergic reactions and transfusion-associated circulatory overload,[16] and shorter time to transfusion. Moreover, FV in transfused plasma may undergo rapid neutralization by an autoantibody or alloantibody, and likely explains why approximately 85% of patients with FV autoantibodies fail to respond clinically to plasma transfusions.[2]

No well-defined guidelines exist for the treatment of acquired FV inhibitors. Aside from close follow-up, it is unnecessary to treat asymptomatic patients,[2] with inhibitors resolving in roughly 42% of patients.[10] Transient inhibitors are more commonly associated with surgery (with or without bovine thrombin exposure) compared to those that arise idiopathically.[10]

In bleeding patients who do not respond to PLT transfusions, alternative therapies may be considered including activated prothrombin complex concentrate (aPCC) or activated recombinant FVII (rVIIa).[13] If aPCC or rVIIa were to be administered, it would be more beneficial to use it as an adjunctive therapy with simultaneous PLT transfusion.[17] The FXa supplemented by aPCC or generated by rVIIa may bind to the FVa provided by the concurrently transfused PLTs.[17]

We recommend following the clinical response to PLT transfusions as opposed to measuring FV activity, especially in patients with an antibody. FV is locally released by PLTs at the site of injury; hence, factor activity assays that utilize PLT-poor plasma may not reflect true hemostatic potential.

If possible, any previously reported FV inhibitor eliciting agents must be discontinued.[2] In patients who do not respond appropriately to PLT transfusions, therapeutic plasma exchange or immunoadsorption may be considered for clearance of circulating FV autoantibodies.[5,18] Intravenous immunoglobulin has also been demonstrated to rapidly increase FV activity levels within 3 days.[19] For long-term suppression of autoantibodies, corticosteroids (1 mg/kg/day) can be prescribed initially with the addition of other immunosuppressant therapies (cyclophosphamide, cyclosporine, azathioprine, or rituximab)[5] if there is no initial response to corticosteroids. Corticosteroids alone achieved a sufficient increase in FV levels in 76% of patients (13/17 patients) with non–bovine thrombin-related antibodies.[13] Patients 2 and 3 both had only corticosteroids prescribed with successful elimination of the inhibitor.

In patients who present with thrombosis, the decision to anticoagulate is difficult. It may depend on the location of the thrombus, symptoms associated with the thrombus, residual blood flow, and the bleeding risk of anticoagulation.[20] In our patient who presented with a thrombus of the brachiocephalic vein, we elected not to anticoagulate and targeted treatment toward eradication of the inhibitor. Although this method proved successful in our patient, there are insufficient data to support this practice in other patients who present with thrombosis. However,

if a thrombus does require anticoagulation therapy, risk assessment for bleeding should be performed, and unfractionated heparin may be the best option using an anti-Xa assay to monitor its intensity. FV may have to be supplemented by PLT transfusions at 3- to 5-day intervals.

In conclusion, FV deficiency is rare and may present with a diverse spectrum of symptoms. Irrespective of etiology, we recommend PLT transfusion as the first-line therapy to achieve hemostasis in bleeding patients.

CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

REFERENCES

1. Asselta R, Peyvandi F. Factor V deficiency. Semin Thromb Hemost 2009;35:382-9.
2. Lippi G, Favaloro EJ, Montagnana M, et al. Inherited and acquired factor V deficiency. Blood Coagul Fibrinolysis 2011; 22:160-6.
3. Bouchard BA, Chapin J, Brummel-ziedins KE, et al. Platelets and platelet-derived factor Va confer hemostatic competence in complete factor V deficiency. Blood 2015;125: 3647-51.
4. Thalji N, Camire RM. Parahemophilia: new insights into factor V deficiency. Semin Thromb Hemost 2013;39:607-12.
5. Franchini M, Lippi G. Acquired factor V inhibitors: a systematic review. J Thromb Thrombolysis 2011;31:449-57.
6. Bowman LJ, Anderson CD, Chapman WC. Topical recombinant human thrombin in surgical hemostasis. Semin Thromb Hemost 2010;36:477-84.
7. Duckers C, Simioni P, Spiezia L, et al. Low plasma levels of tissue factor pathway inhibitor in patients with congenital factor V deficiency. Blood 2008;112:3615-23.
8. Duckers C, Simioni P, Spiezia L, et al. Residual platelet factor V ensures thrombin generation in patients with severe congenital factor V deficiency and mild bleeding symptoms. Blood 2010;115:879-86.
9. Javorschi S, Richard-Harston S, Labrouche S, et al. Relative influence of age and thrombotic history on hemostatic parameters. Thromb Res 1998;91:241-8.
10. Knöbl P, Lechner K. Acquired factor V inhibitors. Baillieres Clin Haematol 1998;11:305-18.
11. Kalafatis M, Simioni P, Tormene D, et al. Isolation and characterization of an antifactor V antibody causing activated protein C resistance from a patient with severe thrombotic manifestations. Blood 2002;99:3985-92.
12. Kershaw G, Orellana D. Mixing tests: diagnostic aides in the investigation of prolonged prothrombin times and activated partial thromboplastin times. Semin Thromb Hemost 2013; 39:283-90.
13. Ang AL, Kuperan P, Ng CH, et al. Acquired factor V inhibitor: a problem-based systematic review. Thromb Haemost 2009; 101:852-9.
14. Zhang B. Recent developments in the understanding of the combined deficiency of FV and FVIII. Br J Haematol 2009; 145:15-23.
15. Di Paola J, Nugent D, Young G. Current therapy for rare factor deficiencies. Haemophilia 2001;7 Suppl 1:16-22.
16. Pandey S, Vyas GN. Adverse effects of plasma transfusion. Transfusion 2012;52 Suppl 1:65S-79S.
17. William B. Adjunctive role for recombinant activated factor VII in the treatment of bleeding secondary to a factor V inhibitor. Blood Coagul Fibrinolysis 2010;19:327-8.
18. Fu YX, Kaufman R, Rudolph AE, et al. Multimodality therapy of an acquired factor V inhibitor. Am J Hematol 1996;51: 315-8.
19. De Raucourt E, Barbier C, Sinda P, et al. High-dose intravenous immunoglobulin treatment in two patients with acquired factor V inhibitors. Am J Hematol 2003;74:187-90.
20. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141: e419S-94S.