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Rare Case Report: Acquired Factor V Deficiency With an Idiopathic Inhibitor

Cheng-Chieh Yen[1], Shih-Feng Cho[2], Daw-Yang Huang[3,4], and Hung-Chun Chen[3,4]

[1]Division of Nephrology, Department of Internal Medicine, Ditmansion Medical Foundation Chia-Yi Christian Hospital, Chia-Yi, Taiwan;
[2]Division of Hematology and Oncology, Department of Internal Medicine,
[3]Division of Nephrology, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan;
[4]Faculty of Renal Care, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan

Abstract

Acquired factor V deficiency is a rare disorder caused by inhibitor formation of idiopathic origin, bovine protein exposure, antibiotics, infection, malignancy, autoimmune disease, transfusion, or pregnancy. The disorder has variable clinical manifestations. The optimal treatment modality of acquired factor V deficiency is not fully determined. The use of plasmapheresis, a suggested treatment, is seldom reported. We herein describe the case of an 83-year-old woman with incident impression of acquired factor V deficiency with an idiopathic inhibitor. Her coagulopathy responded poorly to fresh frozen plasma, single-donor platelets, and steroids. Active gastrointestinal bleeding was noted and supposed by acquired factor V deficiency during admission. Plasmapheresis resolved her active bleeding and coagulopathy. Clinicians should consider plasmapheresis when treating acute haemorrhagic events in patients with acquired factor V deficiency. Further investigation is required to establish the optimal dose and treatment course of plasmapheresis. (J Intern Med Taiwan 2016; 27: 97-102)

Key Words: Acquired factor V deficiency, Idiopathic factor V inhibitor, Plasmapheresis

Introduction

Acquired factor V deficiency is a rare disorder caused by inhibitors of multiple origins. Treatment modalities for active haemorrhagic events in patients with the disorder include providing frozen fresh plasma (FFP), single-donor platelets, steroids, and immunosuppressants as well as plasmapheresis. The optimal treatment is unknown because of the rarity of the disorder. We treated a case of acquired factor V deficiency caused by idiopathic inhibitor formation. The active bleeding event of the patient responded poorly to FFP and steroids but was stabilised using plasmapheresis.

Case Presentation

The patient was an 83-year-old woman with a history of end-stage renal disease, diabetes mellitus,

Reprint requests and correspondence：Dr. Cheng-Chieh Yen
Address：Division of Nephrology, Department of Internal Medicine, Ditmansion Medical Foundation Chia-Yi Christian Hospital, No.539, Zhongxiao Rd. 60002, East Dist., Chia-Yi City, Taiwan

hypertension, and dementia. Her previous admissions and outpatient department visits revealed no history of malignant, autoimmune, or hepatic disease. She had been receiving regular haemodialysis three times a week for 2 years. Normal platelet level (120 000-160 000/mL), prothrombin time (PT; 10.9 s), and activated partial thromboplastin time (aPTT; 33.8 s) was recorded at a local haemodialysis clinic. No bleeding tendency was noted under heparinisation (loading dose: 1000U, maintenance dose: 500U/h) in haemodialysis. Her current medication included donepezil, isosorbide dinitrate, monopril, amlodipine, repaglinide, acarbose, theophylline, and calcium carbonate. She reported malaise, dizziness, shortness of breath on exertion, and a near-syncope sensation for several days. Her family reported that the patient exhibited a slow heart rate (approximately 30-40 beats per min) during her blood pressure measurement. She was brought to the emergency department, where complete atrioventricular block was diagnosed using electrocardiography. A permanent pacemaker was indicated because no spontaneous recovery occurred during observation.

After intensive care unit admission, preoperative survey revealed prolongation of both PT (53.6 s) and aPTT (73.7 s), as shown in Figure 1. No obvious bleeding diathesis was observed. No heparin was used in haemodialysis during hospitalisation. Vitamin K1 and FFP were prescribed but the coagulopathy of the patient persisted. A hematologist was consulted and suggested an aPTT mixing test to determine whether coagulant deficiency or inhibitor formation was present. The immediate mixing test showed correction (aPTT: 44.3 s) and a Rosner index score of 21, indicating circulating

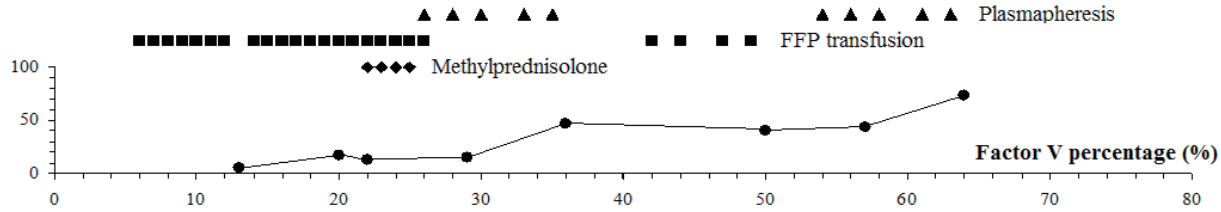

Figure 1a

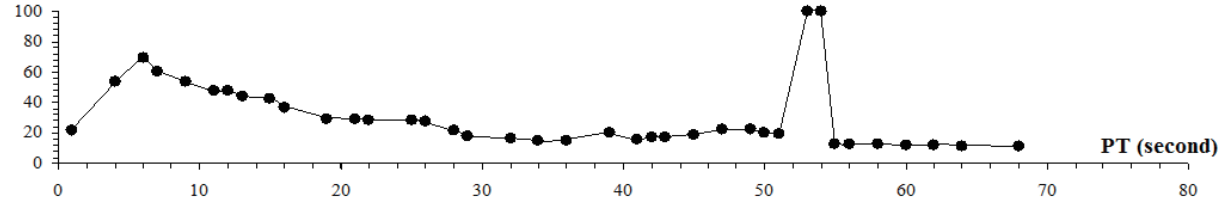

Figure 1b

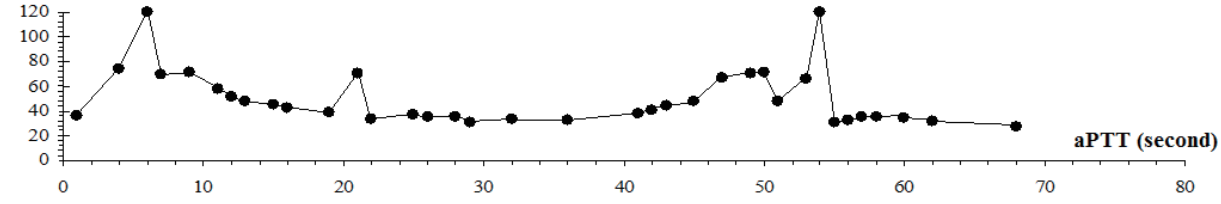

Figure 1c

Figure 1. Summary of acquired factor V inhibitor treatment and responses. Treatments, namely plasmapheresis, FFP transfusion, and methylprednisolone appear at the top of the figure. Responses, namely factor V percentage (Figure 1a), PT (Figure 1b), and aPTT (Figure 1c) appear separately. In each plasmapheresis round, 17–18 units (250 mL/unit) of FFP were exchanged. Methylprednisolone was prescribed at 500 mg qd between days 21 and 24.

inhibitor formation. Anticoagulant tests were all negative. The levels of factors V, VII, VIII, and IX as well as proteins C and S were measured; the only abnormal result was a low factor V percentage (5%). Acquired factor V deficiency caused by inhibitor formation was impressed. FFP, single-donor platelets, and 4-day-pulse therapy with methylprednisolone all failed to resolve the coagulopathy. Active gastrointestinal bleeding with tarry stool passage was found with poor response to FFP transfusion as well as proton pump inhibitor and desmopressin use before methylprednisolone therapy. Factor V deficiency was suspected as the major cause of active bleeding. Immunosuppression was not considered for suspected nosocomial pneumonia at that time. Simultaneously, a first course of plasmapheresis was completed, with 1.5 plasma volume/time (FFP 17 units/time) exchanged once every 2 days, for 5 exchanges in an attempt to lower the titer of the factor V inhibitor. Tarry stool subsided gradually with partially corrected coagulation after plasmapheresis (PT: 14.6 s, PTT: 32.7 s, factor V: 47% of level). We attempted to maintain her coagulation with FFP infusion after remission, but her coagulopathy recurred after plasmapheresis was discontinued. The patient became drowsier, and her infection parameters deteriorated gradually. Severe sepsis with encephalopathy and disseminated intravascular coagulopathy were impressed. Another aPTT mixing test was performed for factor V deficiency follow-up. Normal immediate test (aPTT: 29.7 s, Rosner index: 4) and prolonged 2-hour incubated test (aPTT: 41.3 s) results suggested the formation of a time-dependent inhibitor. The factor V percentage ranged from 40% to 73%, exhibiting no obvious decline. A second course of plasmapheresis was ordered by the intensivist, but the response was poor. The patient died of nosocomial infection of multiple origins such as catheter-related bloodstream infection, pneumonia, and intra-abdominal infection.

Discussion

Factor V, a 330-kDa single-chain polypeptide primarily synthesised in the liver, is a procoagulant factor that involves thrombin production. Wound-site thrombin activates factor V from its inactive form to active form (factor Va). Factor Va involves the formation of the prothrombinase complex and leads to clot formation.[1] The distribution of factor V is mostly in the plasma, with a small proportion in the platelets.[2] Factor V deficiency leads to the prolongation of international normalised ratio INR and aPTT but not of thrombin time. Coagulation factor assays and the Bethesda assay can be used to confirm the diagnosis.[3] In our patient, an aPTT mixing test was performed to distinguish coagulant deficiency (corrected coagulation) from inhibitor formation (noncorrected coagulation). The immediate mixing test showed aPTT correction, and the Rosner index (a test that quantitates the amount of correction to plasma aPTT) was 21 (>15), suggesting that coagulant deficiency was related to inhibitor formation. Tests for lupus anticoagulant, cardiolipin antibodies, factor VIII inhibitor (<0.05 Bethesda units), and factor IX inhibitor (<0.05 Bethesda units) were all negative. The only abnormal measurement was a low factor V percentage (5%). Factor V deficiency with inhibitor formation was impressed. The disorder can further be divided as inherited or acquired; previous normal coagulatory data may suggest the acquired form of the deficiency, as was the case in our patient.

Acquired factor V deficiency is a relatively rare disorder, caused by the development of inhibitors against factor V. Although 3 mechanisms, namely spontaneous autoantibodies, alloantibodies, and cross-reacting antibovine factor V antibodies, have been hypothesised, the precise mechanisms of inhibitor development remain unknown.[4] The inhibitors may be associated with surgical procedures, antibiotics, bovine protein exposure, infec-

tion, malignancy, autoimmune disease, transfusion, or pregnancy, though most inhibitors are idiopathic.[5] None of the medications of our patient has been reported for factor V inhibitor formation. No associated underlying malignancy or autoimmune disease, previous blood transfusion or bovine-like surgical material was traced. Therefore, acquired factor V with idiopathic inhibitor formation was impressed.

The clinical manifestations of acquired factor V deficiency are wide-ranging.[6] For asymptomatic patients with only laboratory abnormalities, no specific treatment appears necessary. If an acute haemorrhagic event occurs, then the focus of treatment is on controlling the bleeding and reducing the inhibitor titer, similar to the management of other factor inhibitors. Blood products, including FFP, platelets, and activated prothrombin complex concentrates, have been used successfully for bleeding control. Steroids, cytotoxic therapy, intravenous immunoglubulin, rituximab, and plasmapheresis have been reported for reducing the inhibitor titer.[3,7] However, the optimal treatment modalities are not fully determined.[8] FFP is frequently given but is usually ineffective. Platelets provide a sequestered source of the cofactor, but this has not been consistently observed.[9] Activated prothrombin complex concentrates have been successfully used but are expensive.[10] Steroids are the most commonly used first-line medicine for treating factor V inhibitors because of their wide accessibility and low cost, but undesirable results and complications after steroid use must be evaluated carefully. Immunosuppressants and rituximab have been shown to be highly tolerable and effective in previous case reports but to also be associated with risk of immunosuppression-related infection.[7,11,12] Our patient, who had end-stage renal disease, received esophagogastroduodenoscopy after tarry stool subsided, revealing only mild reflux esophagitis without active ulceration bleeding. Uremic bleeding was also ruled out because of a negative finding for angiodysplasia and the failure of DDAVP therapy. Steroid-related gastrointestinal bleeding did not favour because of the clinical course. Therefore, we infer that her active gastrointestinal bleeding was mostly related to her acquired factor V deficiency. Her coagulopathy did not initially respond to blood products or steroids, and immunosuppression or rituximab soon after steroid therapy failure during her prolonged hospitalisation would have been overly dangerous. Considering the condition of the patient, plasmapheresis was performed to stop her active bleeding.

Plasmapheresis is one option for treating acquired factor V deficiency. Zehnder et al. first used plasmapheresis to treat a 65-year-old patient exposed to topical bovine thrombin.[13] Previous case series have suggested that plasmapheresis might be one of the most effective therapies for treating acquired factor inhibitors, but similar case reports have seldom been published afterwards.[8] Plasmapheresis is superior to simple plasma or platelet transfusions because it enables the administration of large volumes of plasma containing factor V over a short period of time to neutralise the inhibitory activity without the risk of volume overload that accompanies simple transfusions.[9] In our patient, the first plasmapheresis course successfully resolved her bleeding but only partially corrected her coagulopathy. In our opinion, evidence of the efficacy of plasmapheresis for acquired factor V deficiency is based on case reports and series because of the rarity of the disorder. The recommended dose of FFP and treatment course is difficult to evaluate. Because our patient had acquired factor V deficiency with an idiopathic inhibitor, which has the least favourable outcomes of all acquired factor V inhibitors,[8] the recommended dose and course of plasmapheresis seemed inadequate for her. In addition, evidence is lacking that factor V inhibitor should be treated according to the guidelines on the use of therapeutic apheresis.[14] Further investigation is required to verify the efficacy, optimal FFP dosage, and treat-

ment course of plasmapheresis.

We administered the second course of plasmapheresis approximately 20 days after the first course. However, the result was limited for several reasons. First, nosocomial- and catheter-related infection because of her prolonged hospitalisation could have caused the coagulopathy itself and limited the efficacy of plasmapheresis. Second, we continued administering blood transfusions and antibiotics during admission, which might have related to the inhibitor formation. Third, a second aPTT mixing test and a prolonged 2-hour incubated mixing test suggested time-dependent inhibitor formation. However, it did not favour the factor V inhibitor because the percentage of factor V exhibited no obvious decline (40%-73%).

In our opinion, this case confirmed the role of plasmapheresis in acute haemorrhagic control of acquired factor V deficiency, though disadvantages such as procedure-related bleeding, allergies, and infections from blood products should be considered. Clinicians should consider plasmapheresis when treating acute haemorrhagic related to this disease. More investigation is required to determine its optimal dose and treatment course.

Conclusion

In summary, we treated a case of acquired factor V deficiency caused by idiopathic inhibitor formation. The patient's coagulopathy, suspected to be related to factor V deficiency, responded poorly to FFP, steroids, and other treatments. Her active bleeding event stabilised after plasmapheresis was administered. Clinicians should consider plasmapheresis when treating acute haemorrhagic events in patients with acquired factor V deficiency. Further investigation is required to determine the optimal dose and treatment course of plasmapheresis.

References

1. Ferguson JJ, Waly HM, Wilson JM. Fundamentals of coagulation and glycoprotein IIb/IIIa receptor inhibition. Eur Heart J 1998; 19 (Suppl D): D3-9.
2. Huang JN, Koerper MA. Factor V deficiency: a concise review. Haemophilia 2008; 14: 1164-9.
3. Ortel TL. Clinical and laboratory manifestations of anti-factor V antibodies. J Lab Clin Med 1999; 133: 326-34.
4. Morris CJ, Curry N. Acquired factor V inhibitor in a critically ill patient. Anaesthesia 2009; 64: 1014-7.
5. Ang AL, Kuperan P, Ng CH, Ng HJ. Acquired factor V inhibitor. A problem-based systematic review. Thromb Haemost 2009; 101: 852-9.
6. Alcantara M, Ducastelle S, Rugeri L, Dargaud Y. [Acquired factor V deficiency: a rare bleeding disorder with variable clinical presentations]. Rev Med Interne 2011; 32: e59-61.
7. Yamada Y, Miyakawa Y, Sawano M, Okano Y. Successful treatment of severe lung hemorrhage caused by acquired factor V inhibitor with rituximab. Intern Med 2014; 53: 1083-5.
8. Knobl P, Lechner K. Acquired factor V inhibitors. Baillieres Clin Haematol 1998; 11: 305-18.
9. Fu YX, Kaufman R, Rudolph AE, Collum SE, Blinder MA. Multimodality therapy of an acquired factor V inhibitor. Am J Hematol 1996; 51: 315-8.
10. Vickars LM, Coupland RW, Naiman SC. The response of an acquired Factor V inhibitor to activated Factor IX concentrate. Transfusion 1985; 25: 51-3.
11. Lian EC, Larcada AF, Chiu AY. Combination immunosuppressive therapy after factor VIII infusion for acquired factor VIII inhibitor. Ann Intern Med 1989; 110: 774-8.
12. de Raucourt E, Barbier C, Sinda P, Dib M, Peltier JY, Ternisien C. High-dose intravenous immunoglobulin treatment in two patients with acquired factor V inhibitors. Am J Hematol 2003; 74: 187-90.
13. Zehnder JL, Leung LL. Development of antibodies to thrombin and factor V with recurrent bleeding in a patient exposed to topical bovine thrombin. Blood 1990; 76: 2011-6.
14. Schwartz J, Winters JL, Padmanabhan A, et al. Guidelines on the use of therapeutic apheresis in clinical practice-evidence-based approach from the Writing Committee of the American Society for Apheresis: the sixth special issue. J Clin Apher 2013; 28: 145-284.

罕見病例報告：不明抗體引起之後天性第五凝血因子缺乏症

顏正杰[1] 卓士峯[2] 黃道揚[3,4] 陳鴻鈞[3,4]

[1]戴德森醫療財團法人嘉義基督教醫院 內科部腎臟內科
高雄醫學大學附設中和紀念醫院 [2]內科部血液腫瘤內科 [3]內科部腎臟內科
[4]高雄醫學大學 腎臟照護學系

摘 要

後天性第五凝血因子缺乏症為一種罕見疾病，成因為第五因子抗體的形成，抗體的種類大部分未明，其他如接觸牛型蛋白物質、抗生素、感染、惡性腫瘤、自體免疫疾病、妊娠、輸血或妊娠等也可能產生抗體。最適合的治療方式目前尚無定論，血漿置換術為較少被報導的有效治療方式之一。此病例報告描述一位臨床上診斷為後天性第五凝血因子缺乏症的婦人，使用冷凍新鮮血漿、血小板和類固醇都無法有效改善其凝血功能異常，最後是以血漿置換術成功改善其急性胃腸道出血和凝血功能異常。建議臨床上可考慮使用血漿置換術控制此類病患的急性出血事件，臨床上亦需要後續的研究以確立其最合適的交換血漿容量和治療時間。