Case Report

Rare Coagulopathies in Hematologic Spotlight: Isolated Factor V Deficiency and Combined Factor V and VIII Deficiency

Abstract

Rare coagulation disorders pose significant diagnostic challenges emphasizing the importance of clinical vigilance and meticulous hemostatic workup for accurate diagnosis and timely management. We present two cases of exceptionally uncommon coagulopathies – isolated factor V deficiency (F5D) and combined factor V and VIII deficiency (F5F8D). Case 1 features a 24-year-old woman incidentally diagnosed with severe F5D during routine preoperative evaluation for an ovarian cyst. Despite the absence of any reported bleeding manifestations, a timely and accurate diagnosis was rendered. Perioperative management with fresh frozen plasma and postoperative monitoring ensured favorable surgical outcomes. Case 2 features a 10-year-old male presenting with prolonged gum bleeding. Following systematic hemostatic workup, a diagnosis of F5F8D was rendered, thereby guiding optimal therapeutic interventions. We herein aim to contribute valuable insights into the understanding of coagulation physiology and the diagnostic intricacies and management strategies of rare coagulation disorders.

Keywords: *Factor V and VIII deficiency, factor V deficiency, hemostasis*

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Introduction

Coagulopathies form a spectrum of hematological disorders that range from common conditions such as hemophilia to much rarer entities that challenge our understanding of the physiology of coagulation pathways. Studies of rare coagulation disorders serve as reminders of the importance of clinical vigilance and meticulous hemostatic workup. One such rare condition is "Isolated Factor V deficiency (F5D)," marked by its rare incidence of 1 in 1 million.[1-3] The condition is also known as "Parahemophilia" or Owren's disease.[4] It is distinctly characterized by a deficiency in factor V activity and antigen level or a dysfunctional factor V protein. It is important to note that the presentation can vary widely, ranging from mild bleeding episodes to more severe internal bleeding.[1] Some affected individuals may remain asymptomatic, with the condition being incidentally identified through laboratory investigations performed for other reasons. This necessitates a nuanced understanding and clinical vigilance for accurate diagnosis and management of this uncommon coagulopathy. Combined factor V and VIII deficiency (F5F8D) is an even rarer condition. It involves genetic factors that influence the intracellular transportation of both factors V and VIII.[5] A thorough assessment to comprehend the clinical manifestations of this combined deficiency is imperative for timely diagnosis and optimal therapeutic approach.

We herein report the exceptional encounters of two rare coagulopathies such as F5D and F5F8D. This case report aims to shed light on the significance of systematic hemostatic workup in identifying uncommon coagulopathies, thereby contributing insights into diagnostic intricacies and therapeutic considerations.

Case Reports

Case 1

A 24-year-old woman presented to the surgical department with complaints of abdominal discomfort localized to the right lower quadrant. The patient also had symptoms of giddiness, palpitation, and mild exhaustion. She had third-degree consanguineous marital status with a history of two therapeutic abortions, one because of ectopic pregnancy and the other due to

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intrauterine fetal growth restriction. Her menstrual history was uneventful. Initial clinical evaluation and imaging studies pointed to the presence of an enlarged simple cyst of the right ovary. Complete blood counts and baseline coagulation studies were performed as part of routine preoperative evaluation.

Baseline screening showed microcytic hypochromic anemia and adequate platelet counts (350 × 10^9/L) with normal platelet morphology on peripheral smear examination. Coagulation tests were carried out in venous blood drawn and gently mixed into a commercially available 3.2% buffered trisodium citrate tube, yielding a 9:1 whole blood to anticoagulant ratio, and transported immediately to the laboratory at room temperature. The sample was allowed to stand for 30 min and then centrifuged at 1500 g for 15 min to obtain platelet-poor plasma (PPP). The baseline plasma coagulation tests performed on ACL TOP 500 automated coagulation analyzer (Werfen/ Instrumentation Laboratory Co., Bedford, MA, USA; EQAS qualified) using PPP revealed prolongation of Prothrombin time (PT) and activated partial thromboplastin time (aPTT), whereas thrombin time (TT) and fibrinogen levels remained within normal limits (using reagent kits from HemosIL - RecombiPlasTin 2G for PT; SynthASil for aPTT; TT for TT; Fib-C for Fibrinogen). This is depicted in Table 1. The coagulation analyzer is equipped with a photo-optical clot detection unit, designed to perform routine coagulation and factor activity assays by measuring the endpoint change in optical density. This instrument was under strict daily quality control measures and getting satisfactory reports in the external quality assessment scheme as well. Liver function tests were within normal limits as compared to the laboratory reference values (total bilirubin – 6.1 μmol/L [ref: 5.1–17 μmol/L]; total protein –68 g/L [ref: 60–83 g/L]; serum albumin – 35 g/L [ref: 34–54 g/L]; aspartate transaminase [AST] – 15 IU/L [ref: 0–32 IU/L]; alanine transaminase [ALT] – 7 IU/L [ref: 0–35 IU/L]; alkaline phosphatase [ALP] – 32 IU/L [ref: 30–120 IU/L]; and gamma-glutamyl transferase [GGT] – 11 IU/L [ref: 0–38 IU/L]).

After these laboratory investigations, the patient was further inquired and was found to have no reported history of any bleeding manifestations. The International Society on Thrombosis and Hemostasis-Bleeding Assessment Tool (ISTH-BAT) score was 0. There was no history of prior use of anticoagulant therapy. No Vitamin K injections were administered previously. There was no significant history of bleeding in the family in the preceding two generations.

This unmatched layer of complexity revealed through routine coagulation studies prompted further evaluation. Subsequently, mixing studies were carried out, which showed correction of PT and aPTT with 1:1 normal pooled plasma (NPP). PT and aPTT were corrected with factor II and factor X (Vitamin K dependent factors) deficient plasma; however, no correction was observed with factor V deficient plasma. The factor V activity was <1% as against that of control. Since combined deficiency of factor V and VIII is known to occur, factor VIII assay was performed, which revealed factor VIII activity to be exceeding 150% compared to the control. These are depicted in Table 1. The case was reported as severe F5D.

The diagnosis prompted surgical reconsiderations for the risk of hemorrhage. For perioperative management, fresh

Table 1: Baseline plasma coagulation test results, mixing studies, and factor assays of case 1

Coagulation test performed	Patient	Control	Reference range
PT-INR	43.6”/3.86	11.1”/0.98	9.43”–12.79”/0.85–1.15
aPTT	160.9”	29.4”	24.54”–34.17”
TT	19.1”	15.8”	14.26”–17.38”
Fibrinogen (g/L)	2.95	3.25	2.17–4.32
Mixing studies			
aPTT based			
½ patient +½ control (NPP)	32.4”		
½ patient +½ factor V deficient plasma	160.1”		
½ patient +½ factor X deficient plasma	36.3”		
PT based			
½ patient +½ control (NPP)	12.1”		
½ patient +½ factor II deficient plasma	14.1”		
½ patient +½ factor V deficient plasma	43.3”		
½ patient +½ factor X deficient plasma	14.3”		
Factor assays	**Patient (%)**		**Control (%)**
Factor V assay	<1		98.9
Factor X assay	84.5		91
Factor VIII assay	>150		104

PT: Prothrombin time; aPTT: Activated partial thromboplastin time; TT: Thrombin time; NPP: Normal pooled plasma; INR: International normalized ratio

frozen plasma (FFP) was transfused 24 h before surgery, to bring factor V level above 20%. Another unit of FFP was transfused 1 h before surgery. The surgery was performed with no hemorrhagic complications. In the immediate postoperative period, factor level was maintained with further FFP transfusions and followed up with factor assay. Postoperative recovery was uneventful.

Case 2

A 10-year-old male child presented with prolonged gum bleeding for 5 days. No history of other skin/mucosal/joint bleeding or deeper bleeding. The patient had a record of prolonged bleeding following injuries since the age of 5 years, necessitating frequent transfusions with FFP. No prior use of anticoagulants/Vitamin K injections. No significant history of bleeding was reported in the family in the two preceding generations. The ISTH-BAT score was 6, necessitating further workup.

Baseline screening tests showed microcytic hypochromic anemia and adequate platelet count (226 × 10^9/L) with normal morphology on peripheral smear. However, baseline plasma coagulation tests (pretest procedures carried out as described in case 1), as illustrated in Table 2, revealed prolongation of PT and aPTT, whereas TT and fibrinogen levels remained within the normal range. Liver function tests were within normal limits (total bilirubin – 6.5 μmol/L; total protein – 72 g/L; serum albumin – 39 g/L; AST – 29 IU/L; ALT – 12 IU/L; ALP – 35 IU/L; and GGT – 14 IU/L).

Mixing studies were carried out, which revealed correction of PT and aPTT with 1:1 NPP. PT was corrected with factor II and X (Vitamin K dependent factors) deficient plasma, however was not corrected with factor V deficient plasma. Factor V activity was 15.3% as against that of the control. Subsequently, factor VIII assay was done. Factor VIII activity was 30.7% as against that of control. These are illustrated in Table 2. The case was reported as F5F8D. Since the patient had been receiving frequent FFP transfusions with the latest transfusion administered 3 days before presentation, a repeat factor assay was advised to accurately establish the baseline factor levels. However, the patient did not follow up thereafter for repeat testing.

Discussion

The ISTH-BAT is a standardized questionnaire used to assess and quantify bleeding symptoms. Various parameters such as the frequency, severity, and localization of bleeding episodes are evaluated and scored based on their significance. A score >4 is considered abnormal in adult males, >6 in adult females, and >3 in children, prompting further investigation. A score <2 makes a bleeding disorder unlikely.[6] However, in case 1, despite having a BAT score of zero, further assessment was carried out owing to the incidentally detected abnormal baseline screening coagulation tests. In a study assessing hemostatic abnormalities in preoperative patients, the prevalence of hemostatic abnormalities without reported bleeding symptoms on the ISTH-BAT questionnaire was 10.5%.[7] Another study assessing the utility of the score in South Indian patients showed that the proportion of patients with abnormal scores was higher in secondary (88.7%) than primary (69%) hemostatic defect groups.[8]

The two case reports presented to highlight the rarity and clinical-laboratory intricacies associated with F5D and F5F8D. These coagulopathies, occurring at an incidence of 1 in 1 million cases each, pose unique challenges in diagnosis and management.[2,3,9] In both cases, diagnoses were established after ascertaining the liver function tests and fibrinogen levels to be within normal limits, and Vitamin K-dependent clotting factor levels to be normal (as determined by mixing studies with factor II and factor X deficient plasma, although TT was in high normal range),

Table 2: Baseline plasma coagulation test results, mixing studies, and factor assays of case 2

Coagulation test performed	Patient	Control	Reference range
PT-INR	18.6”/1.67	11.1”/0.98	9.43”–12.79”/0.85–1.15
aPTT	56.0”	29.4”	24.54”–34.17”
TT	17.7”	15.8”	14.26”–17.38”
Fibrinogen (g/L)	2.17	3.25	2.17–4.32
Mixing studies			
aPTT based			
½ patient +½ control	36.7”		
PT based			
½ patient +½ control	12.3”		
½ patient +½ factor II deficient plasma	14.0”		
½ patient +½ factor V deficient plasma	19.3”		
½ patient +½ factor X deficient plasma	15.8”		
Factor assays	**Test (%)**		**Control (%)**
Factor V assay	15.3		103.7
Factor VIII assay	30.7		90.9

PT: Prothrombin time; aPTT: Activated partial thromboplastin time; TT: Thrombin time; INR: International normalized ratio

making the suspicion of liver disease/Vitamin K deficiency unlikely.

The case of F5D underscores the rarity of this coagulopathy, with around 200 cases reported worldwide.[10] Typically characterized by a simultaneous deficiency in both factor V activity and antigen levels (type 1) or a dysfunctional factor V protein despite normal antigen levels (type 2).[11] This disorder manifests with symptoms of varying severity, ranging from being asymptomatic to manifesting life-threatening hemorrhages. Based on the severity, F5D can be categorized as mild (>10% of normal activity), moderate (1% to 10% of normal activity), and severe (<1% of normal activity).[11]

The patient in our case 1 presented with no bleeding symptoms despite severe deficiency (<1% factor activity), emphasizing the need for clinical vigilance in identifying such cases. The presentation in our case supports that the bleeding tendency correlates greatly with platelet levels of factor V over plasma levels and that even patients with a severe deficiency do not completely lack the factor V. Platelet degranulation at the site of injury releases factor V at the site of vascular injury, thereby increasing the local concentration of factor.[12]

The general management approach of F5D involves addressing the bleeding manifestations through antifibrinolytics and FFP administration, given the nonavailability of commercial factor V concentrate.[1,13] Perioperative management in these cases is challenging, as the risk for hemorrhage is higher. Transfusion of FFP and maintenance of factor level between 15% and 20% throughout the perioperative period is imperative to prevent hemorrhagic accidents during surgical procedures.[14] Postoperative daily screening for factor level is advisable for moderation of FFP transfusion and surveillance. The management strategy employed in our case involved transfusion of FFP to proactively address the deficiency and elevate the factor V level above 20%, followed by administration of another additional unit of FFP 1 h before surgery to further bolster the factor levels and reduce the likelihood of intraoperative bleeding. Close monitoring of factor levels in the immediate postoperative period and transfusion of FFP as needed ensured minimizing the risk of delayed bleeding and supporting ongoing hemostasis. The outcome of this approach was favorable, without any perioperative bleeding complications.

The second case report features F5F8D, a rare autosomal recessive coagulopathy. To the best of our knowledge, around 200 cases have been reported in the literature.[15] The disorder involves the LMAN1 and MCFD2 genes responsible for the intracellular transportation of factors V and VIII.[5,16] Simultaneous decrease in the serum levels of these factors below 30% each is diagnostic of F5F8D.[17] Clinical manifestations vary from mild symptoms such as easy bruising and epistaxis to critical bleeding incidents in the gastrointestinal tract and central nervous system.

Management is concerned restoration of factor levels with FFP, desmopressin, and recombinant factor VIII concentrates.[13] Preoperative patients with factor levels below 5% should be managed such as cases of hemophilia A, with the maintenance of factor levels above 30% throughout the surgery and in the postoperative period.[18] Notably, the patient in our case had been receiving frequent FFP transfusions, emphasizing the importance of confirming baseline factor levels, when evaluated after such interventions. The current bleeding episode in our case was managed by the administration of FFP and factor VIII concentrates. The patient was advised to follow up on demand.

Molecular testing could not be carried out in our case. Familial screening of index cases and preconceptional carrier screening are effective approaches for molecular testing. Identification of LMAN1 and MCFD2 genes may also provide a potential target for novel anticoagulant therapies in future.[16]

Conclusion

Isolated F5D and F5F8D are exceedingly uncommon coagulation disorders, which necessitate a more vigilant approach in clinical practice. Implementing a comprehensive coagulation assessment is pivotal for accurate diagnosis. Making timely confirmatory diagnosis becomes imperative for the initiation of appropriate management strategies, offering the potential for relatively favorable patient outcomes.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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