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A Rare Cause of Isolated Prolonged Activated Partial Thromboplastin Time: An Overview of Prekallikrein Deficiency and the Contact System

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Abstract

Prekallikrein (PK) deficiency, also known as Fletcher factor deficiency, is a very rare disorder inherited as an autosomal recessive trait. It is usually identified incidentally in asymptomatic patients with a prolonged activated partial thromboplastin time (aPTT). In this article, we present the case of a 52-year-old woman, with no prior personal or family history of thrombotic or hemorrhagic disorders, who was noted to have substantial protracted aPTT through the routine coagulation assessment before a kidney biopsy. The patient had an uneventful biopsy course after receiving fresh frozen plasma (FFP). Laboratory investigations performed before the biopsy indicated normal activity for factors VIII, IX, XI, XII, and von Willebrand factor (vWF) as well as negative lupus anticoagulant (LA) screen. The plasma PK assay revealed low activity at 15% consistent with mild PK deficiency. The deficit of PK is characterized by a severely prolonged aPTT and normal prothrombin time (PT) in the absence of bleeding tendency. PK plays a role in the contact-activated coagulation pathway and the inflammatory response. Thus, other differential diagnoses of isolated prolonged aPTT include intrinsic pathway factor deficiencies and nonspecific inhibitors such as LA. We concluded that the initial evaluation of a prolonged aPTT with normal PT should appraise the measurement of contact activation factors and factor inhibitors. PK deficiency should be considered in asymptomatic patients with isolated aPTT prolongation, which corrects on incubation, with normal levels of the contact activation factors and factor inhibitors.

Keywords

prekallikrein deficiency, Fletcher factor deficiency, kallikrein-kinin system, activated partial thromboplastin time, prolonged aPTT

Introduction

The contact factor system (also called the kallikrein-kinin system) consists of 2 zymogens, factor XII and prekallikrein (PK), and 1 cofactor, high-molecular-weight kininogen (HMWK).[1] These proteins are involved in blood coagulation, fibrinolysis, complement activation, renin-angiotensin hormonal regulations, and bradykinin formation. Initially, these proteins were thought to have a role in homeostasis due to the prolonged activated partial thromboplastin time (aPTT) related to factor XII, PK, and HMWK deficiency. This was proven incorrect due to the lack of a bleeding tendency seen in these factor deficient patients. However, studies suggest that a role in thrombosis independent of hemostasis is possible.[2] In recent years, significant evidence has emerged implicating a role for these coagulation factors in tissue repair, inflammatory response, and innate immune system.[3,4] In the normal state, the plasma kallikrein-kinin system contributes to basal bradykinin formation by PK activation for the maintenance of vascular homeostasis. When vessel injury occurs, activation of factor XII through contact activation participates in intravascular thrombus formation.[1]

Hereditary PK deficiency, also known as Fletcher factor (FF) deficiency, is a rare autosomal recessive defect usually diagnosed incidentally during routine coagulation tests demonstrating substantially prolonged aPTT and normal prothrombin time (PT) without associated bleeding diathesis.[5,6] This condition is exceedingly rare; thus, the characterization of its phenotype is not well elucidated. In this article, we present the case of an asymptomatic 52-year-old Black

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woman with a prolonged aPTT revealed during a routine workup before a scheduled procedure. A PK activator assay using patient plasma was consistent with PK deficiency.

Case Presentation

A 52-year-old Black woman was noted to have a prolonged aPTT before her elective kidney biopsy. The patient had been recently diagnosed with Sjögren's syndrome and started on steroids. She then developed acute kidney injury associated with a positive antinuclear antibody (ANA) concerning for systemic lupus erythematosus (SLE) complicated by lupus nephritis. She had a history of bulimia with a recent weight gain of 11 kg during the past 2 months. The patient's preprocedure tests revealed a prolonged aPTT of 106.4 seconds (reference interval = 25-32 seconds), with a repeat value of 83 seconds, as well as rapid progression of renal dysfunction with an elevation of creatinine from 1.1 to 1.8 mg/dL in the past 2 months. Given abnormal coagulation laboratories, she was instead admitted for an expedited workup in the setting of rapidly progressive renal dysfunction with a new disorder of coagulation. The patient had normal PT of 10.3 seconds (reference interval = 9.4-12.5 seconds), platelet count of 248 000/μL (reference interval = 200-450 000/μL), and fibrinogen level of 212 mg/dL (reference interval = 150-400 mg/dL). Thrombin time was slightly increased (18.7 seconds; reference interval = 12-14 seconds). von Willebrand factor (vWF) antigen test was elevated to 374 IU/dL (reference interval = 50-200 IU/dL). Other laboratory results were notable for stable normocytic anemia (hemoglobin 10.8 g/dL), with iron studies consistent with anemia of chronic diseases (ferritin 729 mg/L, transferrin 197 mg/dL, total iron-binding capacity 256 μg/dL). A mixing study was ordered. The patient presented with high-grade proteinuria, anasarca, hypoalbuminemia, and urine sediment notable for fat droplets and lipid-laden casts, all consistent with acute nephrotic syndrome. Thus, a decision was made to pursue renal biopsy to further understand kidney disease and guide treatment.

Her current medication list included hydroxychloroquine, torsemide, prednisone, lisinopril, potassium chloride, and sumatriptan. The patient did not have any medical or family history of abnormal hemorrhagic or thromboembolic events. She had an uncomplicated Cesarean section in the past without any bleeding complications. She reported a prolonged aPTT of around 200 seconds in her sister, found incidentally through routine laboratory tests before shoulder surgery, without further hematology follow-up. The patient's physical examination did not show any evidence of ecchymoses, purpura, or petechiae.

The patient underwent the planned kidney biopsy after receiving 3 units of fresh frozen plasma (FFP) in light of the prolonged aPTT, which corrected the aPTT to 27 seconds. Kidney biopsy pathology showed class V membranous disease as well as evidence of proliferative disease with crescents. Possible causes of isolated prolongation of aPTT were considered, including heparin administration, inherited intrinsic pathway factor deficiencies, including XII, XI, IX, and VIII, factor inhibitors, and von Willebrand disease. The patient's laboratory studies before biopsy indicated normal PT as well as a normal activity of factors VIII, IX, XI, XII, vWF, and HMWK. The lupus anticoagulant (LA) screen was positive, but the confirmatory test was negative. Anticardiolipin antibodies and β-2-glycoprotein 1 (immunoglobulins G and M) levels were normal. The plasma PK assay revealed low activity at 15% consistent with mild PK deficiency (reference interval = normal >50%, mild deficiency = 5% to 49%, severe deficiency ≤5%). The plasma PK was measured indirectly by quantifying the amidolytic activity of kallikrein by using a synthetic chromogenic substrate. Antigenic assays for evaluation of structure or quantity of PK were not available.

Discussion

PK deficiency is an uncommon coagulation disease considered not to be associated with bleeding tendency, despite marked aPTT prolongation. PK is the precursor of plasma kallikrein, a procoagulant and proinflammatory protease, that plays a role in the early stages of the intrinsic pathway of the coagulation cascade.[7] It is synthesized primarily by the liver and mainly activated by factor XIIa or other substances such as endothelial cell prolylcarboxypeptidase (PRCP), which functions independently of factor XII.[2,5]

The contact activation of the coagulation pathway is initiated by factor XII that is activated to XIIa via binding to ("contact" with) negatively charged artificial or biological surfaces (contact activation). Factor XIIa proteolytically activates PK to form plasma kallikrein. Kallikrein, then, accelerates the activation of factor XII. This feedback loop amplifies factor XIIa and PK production. Additionally, HMWK binds to PK and factor XI to facilitate their activation (Figure 1).[2,3] Factor XIIa also activates factor XI, leading to thrombin generation, fibrin formation, and platelet activation. Essentially, factor XIIa initiates the intrinsic pathway of coagulation via its substrate, factor XI, and leads to the liberation of the proinflammatory mediator bradykinin by activation of the kallikrein-kinin system.[8] The contact factor deficiencies do not result in a pronounced bleeding tendency as factor XI is additionally activated by platelets and thrombin.[9]

Furthermore, PK is an important mediator of the inflammatory response.[10] Thus, the kallikrein-kinin system can result in an inflammatory response via plasma kallikrein cleaving HMWK and releasing bradykinin. Bradykinin then binds to its constitutively expressed B1 (or B2) receptors. Activation of these receptors in return modulates endothelial cell proliferation, increases vascular permeability, resulting in vasodilation, edema, and hypotension (Figure 1). This system can be activated either by factor XIIa formation or independently formed by PRCP.[1,2]

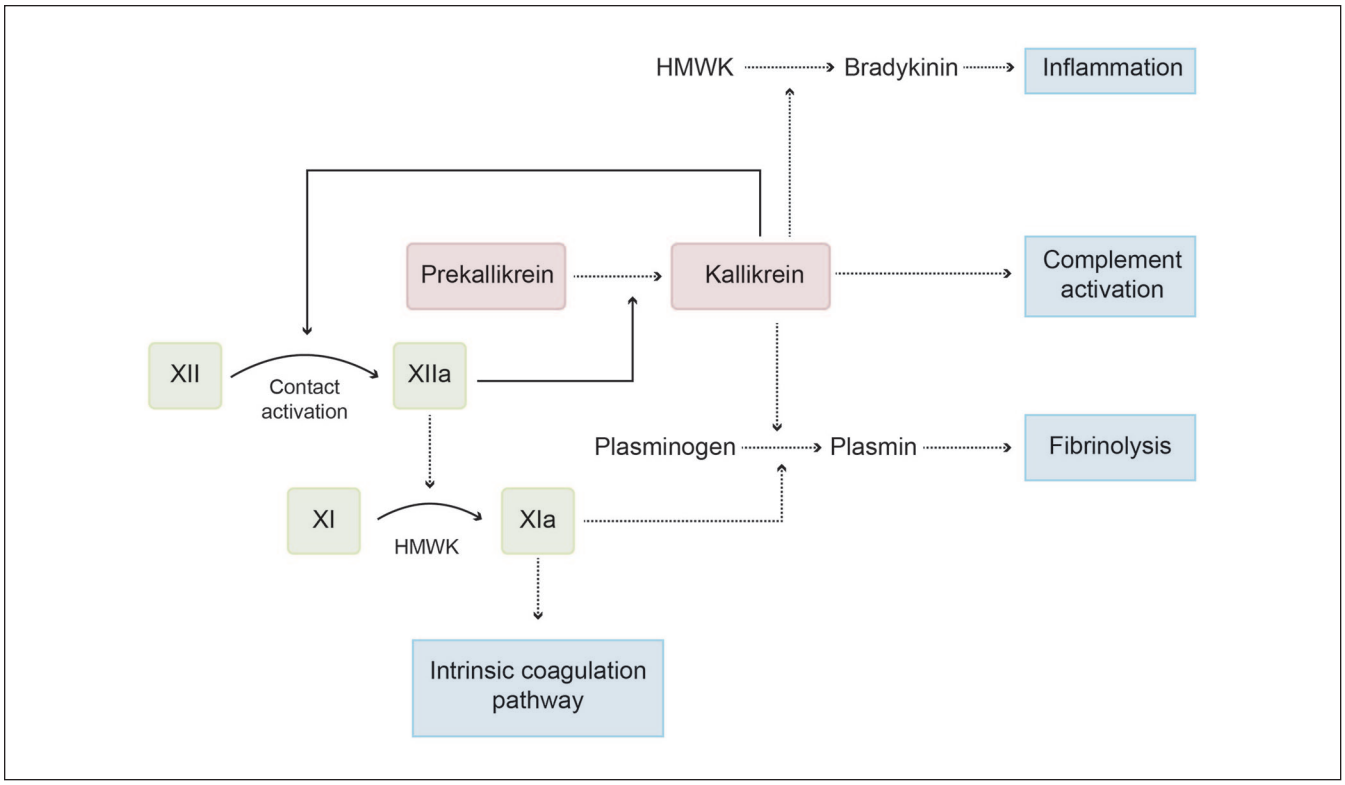

Figure 1. Overview of the contact activation system and the kallikrein-kinin system. Prekallikrein has a role in the initiation of the blood anticoagulation, fibrinolysis, and kinin formation. XII, factor XII; XIIa, factor XII activated; XI, factor XI; XIa, factor XI activated; HMWK, high-molecular-weight kininogen.

It is known that PK deficiency is caused by mutations in the *Klkb1* gene, located on chromosome 4q34-35, that are inherited via an autosomal recessive pattern.[5,6] A homozygous point mutation (C529Y) has been identified as the genetic basis in severe cases.[11] Hereditary PK deficiency was first described in 1965 by Hathaway et al who noted prolonged aPTT among the children of the Fletcher family.[12] Initially, it was hypothesized that the prolonged aPTT was due to a missing new plasma thromboplastin factor, termed the "Fletcher factor." The identity of the FF remained a mystery until 1973 when it was correctly recognized as PK, and the deficient plasma demonstrated abnormalities in the kinin, coagulation, and fibrinolytic systems. This discovery marked for the first time the interrelationship between these systems.[10]

In PK deficiency, the activation process of factor XII occurs in a slow manner resulting in prolonged aPTT.[5] The aPTT is a test for assessing the intrinsic and common pathways of the coagulation cascade from the contact phase system activation to fibrin formation.[13,14] In this assay, the plasma is preincubated with an activator of the contact phase system (ie, silica, celite, kaolin, ellagic) to provide a negatively charged surface and a so-called partial thromboplastin (phospholipids, ie, cephalin). During the preincubation of plasma with the aPTT reagents (activated "surface" and partial thromboplastin), the contact phase of the blood coagulation is activated. Subsequently, the plasma is recalcified and the clotting time is measured.[15] In the Fletcher trait, the aPTT autocorrects on prolonged incubation (after 1 hour) at room temperature (37 °C).[2,13] This phenomenon is unique to PK deficiency and can be explained by the factor XII autoactivation instead of the faster kallikrein-mediated factor XIIa generation in a healthy person. Factor XIIa then activates factor XI, which leads to factor IXa determining the clotting time. PK cofactor is necessary for factor XIIa–mediated factor XIa, hence the failure to normalize aPTT in prolonged incubation time in PK deficiency patients.[2]

Possible causes of elevated aPTT include deficiencies of factors VIII, IX, XI, vWF, PK, or HMWK and nonspecific inhibitors such as LA.[14] The correction of the aPTT test after FFP administration supports the diagnosis of a factor deficiency in our patient and argues against the presence of a factor inhibitor.

In PK deficiency, the aPTT will correct to normal ranges with the addition of an equal volume of normal plasma after prolonged incubation.[16] The rationale for administering FFP for abnormal coagulation stems from the fact that plasma is a depot of all coagulation factors. Plasma doses of 10 to 15 mL/kg typically result in an increase in coagulation factors by 15% to 20%, which reaches levels needed for normal hemostasis. Also, the effect of FFP replacement depends on the starting level of coagulation factors. For

Table 1. Studies Reporting on Cases of Prekallikrein Deficiency.

Case	Year of publication	Author	Age (years)/sex	Incidental finding of isolated prolonged aPTT prior to surgical or dental procedure	Degree of aPTT prolongation (reference values, seconds)	PK assay result and method	Outcome
1	2021	This case	52/Female	Yes	106.4 (25-32)	PK:C 15% (normal ≥ 50%, mild = 5 to 49%, severe = <5%)	aPTT normalized after 3 unit of FFP
2	2020	Barco et al[19]	68/Female	Yes	N/A	PK:C <1%	Surgery without complication
3			17/Male	Yes	N/A	PK:C <1%; PK:Ag 10% (by ELISA)	N/A
4			26/Male	Yes	N/A	PK:C <1%[a]	Surgery without complication
5	2002	Asmis et al13	71/Male	Yes	422 (40-60)	PK:C 5%; PK:Ag 2%[a] (by immunoblotting and autoradiography)	Splenectomy without complication
6	2003	Lombardi et al[20]	14/Male	Yes	110 (32-42)	PK:C <1%[a]; PK:Ag trace (by electroimmunoassays)	Surgery without complication
7	2003	Shigekiyo et al[21]	47/Male	Yes	N/A	PK:C <1%; PK:Ag 25% (by Laurell's method with rabbit antihuman plasma kallikrein sera)	N/A
8	2004	Jones et al[22]	79/Male	Yes (presented with unstable angina)	125 (24-36)	PK:Ag <5%[a] (by ELISA)	Coronary angiography and subsequently, coronary artery bypass grafting without complication
9	2007	Katsuda et al[23]	53/Male	Yes	135.6 (40-100)	PK:C <1%	N/A
10			64/Female	Case 9's family member	136.5 (40-100)	PK:C 0.9%	N/A
11			50/Female	Case 9's family member	126.2 (40-100)	PK:C 3%	N/A
12	2007	Francois et al[11]	63/Male	Yes (admitted for ischemic stroke with carotid atherosclerosis)	176 (<35)	PK:C <1%; PK:Ag 7% (by ELISA)	N/A
13			38/Female	Yes (admitted for second-trimester pregnancy loss)	186 (<35)	PK:C <1%; PK:Ag 7% (by ELISA)	Curettage without complication
14	2009	Nagaya et al[24]	69/Female	Presented with purpura and subcutaneous hematoma	64.9 (27.5-42.1)	PK:C <1%[a]	N/A
15	2009	Maak et al[25]	14/Male	Yes	96 (24-36)	PK:C <1%	N/A
16	2010	Girolami et al[26]	40/Male	Yes (presented with idiopathic deep vein thrombosis)	96 (32-38)	PK:C 5%[a]; PK:Ag 95% (ND)	Treated with enoxaparin then warfarin without recurrence
17			57/Female	Case 16's family member	N/A	PK:C 4%[a]; PK:Ag normal (by ELISA)	N/A
18			55/Female	Case 16's family member	N/A	PK:C 4%[a]; PK:Ag normal (by ELISA)	N/A
19	2014	Girolami et al[27]	32/Male	Yes	140 (32-42)	PK:C 1%[a]; PK:Ag <1%[a] (by immunosorbent assay method)	N/A
20	2019	Ryu et al[28]	4/Male	Yes	222 (26.7-37.6)	PK:C <1%; PK:Ag 3% (by ELISA)	Tonsillectomy without complication
21	2017	Criel et al[29]	15/Male	Yes (presented with Ménière's disease)	169 (24.8-34.4)	PK:C <3%	N/A
22	1985	Harris et al[30]	43/Male	Presented with multiple ischemic infarcts	109 (28-42)	PK:C <1%	Treated with heparin then warfarin. Later developed massive brain hemorrhage and expired
23			38/Female	Case 23's family member	105 (28-42)	PK:C <1%	N/A
24	1990	Joggi et al[31]	48/Female	Yes	117 (26-36)	PK:C <1%; PK:Ag <1% (ND)	N/A
25			66/Male	Yes	112 (26-36)	PK:C <1%; PK:Ag <1% (ND)	N/A
26	1991	Hess et al[32]	36/Female	Yes (presented with ischemic stroke at left frontal lobe)	62.2 (25-35)	PK:C <1%	Treated with heparin but developed severe menorrhagia and switched to aspirin without recurrence 8 months after
27	2010	Eeckhoudt et al[33]	50/Male	Yes	140 (23-33)	PK:C <1%[a]	2 units of FFP prior to surgery to bring activated coagulation time down from 316 to 81, to be able to monitor with heparin infusion. No complications after surgery
28	2012	Bojanini et al[34]	32/Female	Recurrent TIA with history of hypertension, hyperlipidemia, with no obvious cause	99.4 (N/A)	PK:C 1%[a]; PK:Ag <1% (ND)	On daily aspirin and hypertension/dyslipidemia medications with close monitoring
29	1982	Raffoux et al[35]	11/Male	Yes	N/A	Fletcher factor level 0.41 U/mL (0.75-1.25 U/mL; ND)	Tonsillectomy was performed with prolonged bleeding, which required transfusion of FFP and several sutures
30	1980	Waddell et al[36]	62/Male	Yes (presented with hematuria from bladder inflammation in the setting of cyclophosphamide use)	78 (N/A)	Fletcher factor clotting assay <1% Radioimmunoassay for PK 1%	aPTT was shortened with FFP presenting persistent hematuria. Later developed scrotal and penile cellulitis not responding to antibiotic and expired
31	1982	Poon et al[37]	7/Male	Presented with 18 months history of frequent epistaxis	355 (N/A)	Fletcher factor clotting assay <0.01% Radioimmunoassay for Fletcher factor assay <0.01%	No abnormal bleeding in 2 years follow-up

(continued)

Table 1. (continued)

Case	Year of publication	Author	Age (years)/sex	Incidental finding of isolated prolonged aPTT prior to surgical or dental procedure	Degree of aPTT prolongation (reference values, seconds)	PK assay result and method	Outcome
32	1990	Castaman et al[38]	22/Female	Yes	Ratio greater than 2	PK:C <1%; PK:Ag negative (by electroimmunoassay)	No improvement in PK level after DDAVP
33	1990	De Stefano et al[39]	49/Female	Yes	116 (<30.6)	PK:C <1%; PK:Ag 50% (by Laurell immunoelectrophoresis)	Total thyroidectomy without complication
34			51/Male	Case 34's family member	120 (<30.6)	PK:C <1%; PK:Ag 34% (by Laurell immunoelectrophoresis)	N/A
35			47/Male	Case 34's family member	94 (<30.6)	PK:C <1%; PK:Ag 34% (by Laurell immunoelectrophoresis)	N/A
36			38/Female	Case 34's family member	110 (<30.6)	PK:C <1%; PK:Ag 54% (by Laurell immunoelectrophoresis)	N/A
37	1970	Hattersley et al[40]	77/Female	Yes	135.9 (<41.0)	Fletcher factor clotting assay <1%[a]	Closed reduction of the fracture without complication
38			6/Male		278.6 (<42.5)		Excision of cervical and axillary nodes without complication
39			50/Male		170.0 (N/A)		Underwent hemorrhoidectomy and polypectomy without complication
40	2009	Odumosu et al[41]	25/Female	Yes	69.4 (24-38)	PK:C <1%	4 units of FFP to correct the prolonged aPTT. Emergency Cesarean section was done without complication
41	2009	van Veen et al[42]	19/Male	Yes	132 (25.5-37.5)	PK:C <1%	Successful redo sternotomy and aortic valve replacement
42	1995	DeLa Cadena[43]	9/Female	Yes	58 (<28)	PK:C <1%; PK:Ag 20–25 (by ELISA)	Dental extraction without complication
43	2003	Dietzel et al[44]	24/Male	Yes	N/A	PK:C <1%; PK:Ag normal (ND)	Renal surgery without complication
44	1980	Saade[45]	29/Male	Yes	67.7 (33-40)	Fletcher factor clotting assay 1%	Minor surgery with ingrowth toenail without complication
45	1983	Colla et al[46]	20/Male	Yes	135 (25-35)	PK: Undetectable (measured by a colorimetric method using a specific chromogenic substrate)	N/A
46	1986	Bouma et al[47]	38/Female	Yes	N/A	PK:C <1%; PK:Ag 35% (ND)	Hysterectomy without complication
47			N/A/Male	Case 47's family member	N/A	PK:C <1%; PK:Ag 34% (ND)	N/A
48			N/A/Male	Case 47's family member	N/A	PK:C <1%; PK:Ag 43% (ND)	N/A
51	2018	Baker et al[48]	15/Male	Yes	50.2 (21-32)	PK:C <5%	FFP 15 mL/kg 1 hour before for normalization of PK and improved monitoring during surgery. Open cardiac surgical repair for ASD without complication
52	1965	Hathaway et al[12]	11/Female	Yes	250 (<100)	First Fletcher factor assay	N/A
53			8/Female	Case 53's family member	208 (<100)		N/A
54			4/Female	Case 53's family member	174 (<100)		N/A
55			9/Male	Case 53's family member	168 (<100)		N/A

Abbreviations: aPTT, activated partial thromboplastin time; PK, prekallikrein; PK:C, prekallikrein clotting assays; FFP, fresh frozen plasma; N/A, not available; PK:Ag, prekallikrein antigen; ELISA, enzyme-linked immunosorbent assay; ND, not described; TIA, transient ischemic attack; DDAVP, desmopressin; ASD, atrial septal defect.

[a]The decreasing/normalization of the aPTT with increasing preincubation time.

instance, if the levels are substantially low (very prolonged aPTT as presented in this patient), the plasma replacement may reflect significant improvement compared with those in whom the levels are mildly decreased.[17] However, this is dependent on the specific sensitivity of the aPTT reagent to PK levels.

The patient also presented with a slightly increased thrombin time. Severe hypofibrinogenemia (<100 mg/dL) can extend the thrombin time. This can result from a complete lack of fibrinogen (afibrinogenemia), decreased amount of fibrinogen (hypofibrinogenemia), or the presence of dysfunctional fibrinogen (dysfibrinogenemia). Acquired conditions, such as liver or renal disease, amyloidosis, thrombolytic therapy, disseminated intravascular coagulation (DIC), malignancy, and thrombin inhibitors (heparin, dabigatran, argatroban, and hirudin), can also lead to reduced fibrinogen levels and hence prolonged thrombin time.[18] Our patient did not present with any of these conditions, and she was not receiving any of these medications. Therefore, the normalization of the thrombin time indicates a likely artifact. It should be noted that despite a dysfibrinogenemia was not completely ruled out, it was unlikely given the normal fibrinogen and the normal postprocedure thrombin time.

Reports of PK deficiency diagnosed as an incidental finding of isolated prolonged aPTT before procedures have been published since 1965 (Table 1). These data have concluded that a clear association with a prothrombotic state or bleeding tendency cannot be made, despite the marked in vitro clotting defect.[13,19,20] Some patients underwent procedures without complications after the correction of aPTT with FFP, as presented in our patient. Although limitations of these cases reported are the lack of consensus about the number of units needed to correct the defect and the heterogeneity of the type of PK assay used. Nevertheless, further research is required to clarify these points.

The case of PK deficiency described in this report was uncovered after the incidental finding of prolonged aPTT during routine presurgical coagulation studies. Our patient was not on any anticoagulation and had no history of hemorrhagic or thrombotic events. Her sister had a similar history of prolonged aPTT that could suggest a mode of inheritance. We concluded that the initial evaluation of a prolonged aPTT with normal PT in the absence of bleeding tendency should appraise the measurement of contact activation factors and factor inhibitors. The clinical scenario of an asymptomatic patient with a prolonged aPTT should raise the possibility of PK deficiency especially if the aPTT corrects on extended incubation.

Author Contributions

Ivy Riano and Klaorat Prasongdee wrote the original draft of the paper. All authors read and approved the final manuscript. All authors had access to the data and a role in writing this manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed Consent

Verbal informed consent was obtained from the patient for her anonymized information to be published in this article.

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