Case Report

Acquired Hypoprothrombinemia Inducing Bleeding in a Girl with Transient Antiphospholipid Antibody: Case Report

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Background: *Congenital or acquired prothrombin deficiency is a rare condition.*
Case Report: *A 2-year-7-month old Thai girl presented with ecchymosis, bleeding at both thighs and right ear lobe after a self-limited viral infection.*
Results: *The investigations revealed prolonged APTT and PT, prothrombin level 6% and positive anticardiolipin antibody 26.2 IU/mL. The 1:1 mixture of her plasma and normal plasma could not normalize her APTT and PT. The inhibitor to prothrombin determined by Bethesda method was 0.62 BU. She was responsive to 20 ml/kg of FFP transfusion, followed by 10 ml/kg at an interval of 12 h for three days and daily 500 units of prothrombin complex concentrate administration for three days. At two-week follow-up, she had no bleeding symptom, coagulation tests were normal, prothrombin level was normalized at 94%, no inhibitor to prothrombin was detected, and anticardiolipin antibody became negative. The additional DNA analysis of her prothrombin gene revealed nine different polymorphisms for which seven had been found in patients with congenital prothrombin deficiency and two were novel (4096T→C, 4097T→C). These single nucleotide polymorphisms are not the disease-causing mutations. In addition, neither known mutations inducing congenital prothrombin deficiency were identified.*
Conclusion: *The acquired hypoprothrombinemia was concluded as the cause of bleeding in this reported patient. It might be caused by the transient low titer of antiphospholipid antibody, which was responsive to replacement therapy of FFP and prothrombin complex concentrate.*

Keywords: *Hypoprothrombinemia, Antiphospholipid antibody, Bleeding tendency, Prothrombin deficiency*

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Prothrombin is a vitamin-K dependent plasma glycoprotein synthesized in the liver. It is encoded by a gene located at the chromosome 11, composed of 14 exons separated by 13 introns. The products of this gene include a signal peptide, a propeptide, a domain rich in γ-carboxyglutamic acid, a short aromatic amino acid stack domain, two kringle domains and the serine protease domain. Prothrombin is a precursor for thrombin through the activation of factor Xa in the presence of factor Va, phospholipid and calcium. Thrombin is an essential enzyme in the coagulation cascade to cleavage fibrinogen resulting in fibrin clot.

Congenital prothrombin deficiency is an extremely rare autosomal recessive bleeding disorder affecting 1:2,000,000 populations[1]. However, several patients with acquired hypoprothrombinemia associated with antiphospholipid antibody syndrome or lupus anticoagulant syndrome have been previously reported[2-4]. Antiphospholipid antibodies are directed against phospholipid protein complex that inhibit phospholipid- dependent coagulation tests inducing prolonged APTT and PT. The presence of antiphospholipid antibody is commonly associated with an elevated risk of venous and arterial thrombosis as well as recurrent miscarriages. Bleeding is a rare manifestation of antiphospholipid antibody syndrome,

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when it occurs; it is nearly always due to hypoprothrombinemia or thrombocytopenia. Here, the authors report acquired hypoprothrombinemia inducing bleeding in a Thai girl with transient antiphospholipid antibody. The clinical manifestations and molecular analysis were illustrated.

Material and Method

Laboratory determination

The coagulation tests of activated partial thrombinplastin time (APTT), prothrombin time (PT) and thrombin time (TT) were determined on the ACL200 Coagulometer (Instrumentation Laboratories, Lexington, MA, USA). The procoagulant activities of factor VIII, X, V and prothrombin were measured using a one-stage method based on the APTT and PT on the ACL200 Coagulometer with the specific factor deficient plasma purchased from Instrumentation Laboratories, Lexington, MA, USA. Fibrinogen was measured by clotting method and D-dimer was determined by D-dimer plus kit purchased from Dade Behring Marburgh GmbH, Germany. Lupus anticoagulant was detected by the combination of APTT, kaolin clotting time, dilute Russell's viper venom time, platelet neutralization procedure and tissue thromboplastin inhibition test as described previously[5]. An inhibitor to prothrombin measurement was modified by using Bethesda method[6]. Anticardiolipin antibody was determined by enzyme-linked immunosorbent assay. Antinuclear antibody was determined by immunofluorescence technique while anti-DNA was determined by fluorescence enzyme immunoassay. Complement of C_3 and C_5 was measured by nephelometry method and finally, C-reactive protein was determined by immunoturbidity method.

Prothrombin gene amplification

Prothrombin gene from exon 1 to exon 14 including 3′ untranslated region was amplified by 12 pairs of previously described primers[7]. Polymerase chain reaction (PCR) was performed in 25 μL reaction volume containing 7.5 pmoles of each primer in 1.5 mM $MgCl_2$, 67 mM Tris-HCl (pH 8.3), 16.6 mM $(NH_4)_2SO_4$, 10 mM β-mercaptoethanol, 100 μg/mL bovine serum albumin, 0.2 mM of each of dNTP and 1.25 unit of DNA polymerase. Approximately 250 ng of DNA was used for amplification. Following an initial denaturation at 94°C for 5 min, 30 cycles of PCR amplification was performed with denaturation at 94°C for 40 seconds, annealing at 58°C for 40 sec and extension at 72°C for 40 sec. The final extension was 72°C for 5 min.

Conformation sensitive gel electrophoresis[8,9]

The technique is based on the detection of heteroduplexes in DNA by their aberrant migration in mild denaturing polyacrylamide gels. Briefly, heteroduplexes were prepared by mixing 5 μL of PCR product from patient with 5 μL of PCR product from a normal control. Samples were denatured by heating to 98°C for 5 min and then incubated at 65°C for 30 min to allow heteroduplex formation. Three microliters of heteroduplexed samples were mixed with 1 μL of loading buffer (0.25% xylene cyanol, 0.25% bromphenol blue, and 50% glycerol in water) and electrophoresed in home-made gel (170 x 500 x 1 mm in size) containing 10% acrylamide [99:1 acrylamide: bis (acrolyl) piperazine], 10% ethylene glycol, 15% formamide and 0.5 x TTE buffer (20 x TTE: 1.78M Tris, 570 mM Taurine, 4 mM EDTA). Polymerization was achieved by the addition of 0.1% ammonium persulfate and 0.07% N, N, N', N'-tetramethylethylenediamine. Following electrophoresis at 550 V for 20 h, bands were visualized by silver staining.

DNA sequencing

Samples displaying abnormal conformation sensitive gel electrophoresis patterns were sequenced by the Big Dye Terminator cycle sequencing V.3.1 kit on the ABI prism 3100 genetic analyzer using the same described primers[7].

Case Report

A previously healthy 2-year and 7-month-old Thai girl presented with low-grade fever and erythrematous rash on trunk for one week, which was spontaneously resolved. She had no family history of bleeding disorders or connective tissue diseases. Three days later, the patient became irritable and refused to stand and to walk even though there was no previous history of trauma. She was admitted at a private hospital in her hometown, 300 km from Bangkok. Physical examination revealed T 37.1°C, BW 13.7 kg, both legs swollen with tenderness and limitation of movement. Complete blood counts revealed Hct 32%, WBC 13,700/μL (PMN 53%, L 34%, E 6%, M 7%), platelet 777,000/μL and ESR was 87 mm/h. Since the infection at the legs could not be excluded, parenteral cloxacillin of 500 mg every 6 h was started. On the second day of hospitalization, the patient was still irritable. The hematocrit dropped to 26%. On the third day of hospital, the coagulation tests were studied and revealed the prolonged APTT and PT. Vitamin K deficiency was suspected, therefore, 10 mg

of vitamin K1 was given intravenously and 20 ml/kg of fresh frozen plasma (FFP) was infused. Due to the high fever and swollen leg, other unusual inflammatory process and other causes of bleeding disorders were investigated. ESR was repeated and was found to increase to 123 mm/h. Additional bleeding time by Duke's method was performed at the right ear lobe revealing prolongation of more than 10 min. The patient had slight improvement shown by occasionally moving her legs. She was referred to Ramathibodi University Hospital in Bangkok for investigation and proper management after being hospitalization for four days.

Physical examination at Ramathibodi Hospital revealed afebrile, BP 103/73 mmHg, P 170/min, markedly pale, purpuric spots at buccal mucosa, ecchymosis at right shoulder and right knee, bleeding from right ear lobe and both thighs swollen. Complete blood counts revealed hematocrit 17.7%, hemoglobin 5.8 g/dL, mean corpuscular volume (MCV) 66 fL (N 80 $\pm$ 5 fl), WBC 13,000/μL (PMN 47%, L 43%, M 8%, E 2%) and platelet 677,000/μL. The peripheral blood smear demonstrated hypochromic and microcytic RBC with normal platelet morphology. The coagulation testings showed prolonged APTT and PT with normalized TT and other laboratory determinations are shown in Table 1. Biochemistry and liver profile were within normal limit. The hemoculture was also taken. The unusual etiology such as autoimmune disease was suspected since the common cause of vitamin K deficiency has already been treated in the provincial hospital. The mixing test of patient's plasma with normal plasma could not normalize the prolonged APTT and PT and the inhibitor to prothrombin determined by the Bethesda method was 0.62 BU. The positive anticardiolipin antibody, anti-nuclear antibody and anti-DNA were found so the presence of antiphospholipid antibody was confirmed. Ultrasonography study of both lower extremities showed multifocal increased echogenicity of muscles in both thighs, a well-defined inhomogenous hypoechoic lesion in subcutaneous fatty tissue of pre-tibial region, measured 0.8 x 0.6 cm at right the leg and a thin layer of fluid 2-4 mm thick in deep subcutaneous fatty tissue on the fascia of the left leg. The fascia itself was thickened. These lesions could be infection, inflammation, or process of bleeding. There was no any ultrasonographic abnormality in both knees and ankles.

The diagnosis of intramural bleeding at both thighs due to acquired hypoprothrombinemia associated with antiphospholipid antibody was concluded. Replacement therapy with packed red cells

Table 1. Laboratory determination of the studied patient

Parameter	Normal range	On admission	FU 2 weeks	FU 6 months	FU 1 year
Hct (%)	36-40	17.7	31.1	38.0	-
Platelet count (/μL)	200,000-400,000	677,000	711,000	461,000	-
APTT (sec)	28-38	65	34.0	30.7	33.5
PT (sec)	10-13	35	12.6	10.5	12.6
TT (sec)	7.5-10.5	11	8.5	10.5	10.2
Fibrinogen (mg/dL)	184-402	366	-	-	-
Bleeding time (min)	2-7	Ivy method 2 min	-	-	-
D-dimer (μg/L)	<300	720	-	-	-
Prothrombin (%)	50-150	6	94	-	116
Factor V:C (%)	50-150	107	-	-	-
Factor VIII:C (%)	50-150	220	-	-	-
Factor X:C (%)	50-150	107	-	-	-
Antibody to prothrombin (BU)	Negative	0.62	-	-	Negative
Lupus anticoagulant (%)	Negative	Negative	Negative	Negative	Negative
Anti-cardiolipin antibody (U/mL)	<15	26.2	Negative	Negative	Negative
Anti-nuclear antibody	<1:80	Coarse speckled 1:80	Negative	-	Negative
Anti-DNA (IU/mL)	0-50	85	Negative	-	Negative
C3 complement (μg/mL)	900-1,800	1,550	-	-	-
C4 complement (μg/mL)	100-400	228	-	-	-
C-reactive protein (mg/L)	0-5	25.6	-	-	-

APTT = activated partial thromboplastin time; PT = prothrombin time; TT = thrombin time; FU = follow-up

10 ml/kg was initially given. Due to the low titer of prothrombin antibody, FFP 10 ml/kg was given. At one hour after FFP infusion, the APTT was slightly shortened from 65.0 to 52.7 sec and PT was slightly shortened from 35.0 to 26.8 sec. At 12 h after FFP, both APTT (68.6 sec) and PT (30.4 sec) became longer. Therefore, FFP 10 ml/kg was given at an interval of 12 h for three days, followed by daily prothrombin complex concentrate 500 units for three days. The swollen thighs gradually decreased and the patient could walk properly after three days and five days of treatment, respectively. In addition, intravenous cloxacillin 500 mg every 6 h was continued for three days and switched to oral cephalosporin after the hemoculture report of no growth. She was discharged home after being hospitalized for seven days and oral iron supplement was prescribed.

Two weeks later at the follow-up visit, the patient had no bleeding symptoms. The complete blood counts showed normal findings except for the low MCV of 65.6 fl. Also, the coagulation tests were repeated and revealed normal. Interestingly, the prothrombin level was normalized at 94% (normal 50-150%), no inhibitor to prothrombin was detected and anticardiolipin antibody became negative. The investigation for thalassemia and hemoglobinopathies was performed at six weeks after iron supplement. Heterozygous hemoglobin E was concluded. Other laboratory determinations repeated at 6-months and one-year follow-up were normal.

In addition, the DNA analysis revealed that no previously reported mutations of congenital prothrombin deficiency was found. Nine different polymorphisms at the patient's prothrombin gene are shown in Table 2. Six polymorphisms (4048 T→C, 4125 C→G, 4203 C→T, 4272 G→A, 4291 A→G, 4298 A→G) have been described among Japanese, Italian an Indian patients with congenital prothrombin deficiency with the level of prothrombin ranging from 4.0 to 17.5%[10-13] while one polymorphism (4304 ins G) has recently been reported in one Indian patient with congenital prothrombin deficiency[7]. The remaining two polymorphisms (4096 T→C, 4097 T→C) were novel. These single nucleotide polymorphisms are not the disease-causing mutations. In addition, neither known mutations inducing congenital prothrombin deficiency were identified.

Discussion

The reported patient has recovered from hypoprothrombinemia after the onset of bleeding for four weeks. She was defined as acquired hypoprothrombinemia, which was previously reported in association with lupus anticoagulant or antiphospholipid antibody (APA) syndrome. The name APA implies that the antibodies are directed toward phospholipids. The APA is found in two broad categories of patients. The first group includes patients with vascular thrombosis and pregnancy morbidity. Their antibodies tend to be high titer, persistent and consist of Ig G or Ig M isotypes. The second group includes patients with little clinical consequence. Their antibodies tend to be low titer, transient and are more often Ig M. It is commonly found in children with histories of infection.

The authors' reported patient was defined in the second group of APA, which might be associated with a self-limited viral infection[14]. However, the patient had transient low level of anticardiolipin antibody but negative lupus anticoagulant. The discrepancy of anticardiolipin antibody and lupus anticoagulant is due to the different physical structure of phospholipids used in the assay. Anticardiolipin antibody recognizes negatively charged phospholipids when they take on a lamellar (plate like) configuration, whereas the lupus anticoagulant reacts more strongly with phospholipids when they assume a hexagonal form[15]. Nevertheless, anticardiolipin antibody had disappeared at the two-week follow-up, which confirmed that the positive APA in the reported patient was transient. She was not diagnosed with APA syndrome according to the "Sapporo criteria"[16,17] which is defined in patients with

Table 2. Nine homozygous single nucleotide polymorphisms found in the studied patient at the kringle-1 region of prothrombin gene

Exon/Intron	Nucleotide mutation
Intron E	T4048C
Intron E	T4096C*
Intron E	T4097C*
Intron E	C4125G
Exon 6	C4203T**
Intron F	G4272A
Intron F	A4291G
Intron F	A4298G
Intron F	4304 ins G

* Novel polymorphisms, not previously reported in http://www.nlm.nih.gov/entrez/query.fcgi?CMD=Details&DB=pubmed

** No change in amino acid of threonine

elevated anticardiolipin antibody levels and/or lupus anticoagulant on two or more occasions at least six weeks apart. However, the transient APA might induce isolated hypoprothrombinemia in this reported patient, which was confirmed by the laboratory testings of detecting low inhibitor titer of 0.62 BU to prothrombin.

There was a discrepancy finding concerning bleeding time. The bleeding time performed by Duke's method at the ear lobe in the first hospital was prolonged (> 10 min) while the modified Ivy's method at the second hospital was normal (2 min). It could be explained by a technical error since the laboratory procedure was performed with an un-cooperative young child with painful legs. Thus they might have encountered difficulty. Ultimately, the Duke's bleeding time is not recommended in the clinical practice[18].

Although steroid administration is the treatment of choice for antiphospholipid antibody, replacement therapy is an alternative. FFP transfusions combined with prothrombin complex concentrate administration were selected due to the low titer of prothrombin antibody and in suspicious of infection. However, they should be given frequently. The half-life of prothrombin is two to four days but the replacement therapy in the present patient was given at an interval of 12 hours with responsiveness. In fact, prothrombin complex concentrate is superior to FFP since it is virus-inactivated product. However, it is more expensive than that of FFP.

The additional DNA analysis confirmed that the patient did not possess mutation causing congenital prothrombin deficiency. On the contrary, nine different polymorphisms were detected. Seven polymorphisms were previously reported in patients with congenital prothrombin deficiency while two polymorphisms were novel. These single nucleotide polymorphisms are not the disease-causing mutations.

In conclusion, the authors report acquired hypoprothrombinemia in a Thai girl with transient APA following a self-limited viral infection. She was responsiveness to the replacement therapy. She had normalized prothrombin level at two-week follow-up period. No recurrence was revealed at one-year follow-up.

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Potential conflicts of interest

None.

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ภาวะโปรทรอมบินต่ำที่เกิดขึ้นภายหลังเนื่องจาก antiphospholipid antibody ที่เกิดขึ้นชั่วคราว ทำให้เกิดอาการเลือดออกในเด็กหญิง: รายงานผู้ป่วย

อุษณรัฐมี อนุรัฐพันธ์, วีระศักดิ์ ศาสนกุล, นงนุช สิระชัยนันท์, ชาญชัย เกษมโกศลศรี, สุภนีวรรณ เชาว์วิศิษฐ, อำไพวรรณ จวนสัมฤทธิ์

ภูมิหลัง: *ภาวะโปรทรอมบินต่ำทางพันธุกรรมหรือเกิดขึ้นภายหลังเป็นภาวะที่พบได้น้อย*
รายงานผู้ป่วย: *เด็กหญิงไทยอายุ 2 ปี 7 เดือน มีอาการจ้ำเขียว เลือดออกที่ต้นขา 2 ข้างและติ่งหูหลังจากหายจากโรคติดเชื้อไวรัส*
ผลการศึกษา: *การตรวจทางห้องปฏิบัติการพบว่ามี APTT และ PT ยาวกว่าปกติ, ระดับโปรทรอมบิน 6%, anticardiolipin antibody 26.2 IU/ml, mixing test ของพลาสมาผู้ป่วยกับพลาสมาคนปกติไม่สามารถทำให้ APTT และ PT สั้นลง และสารต้านต่อโปรทรอมบิน 0.62 BU ผู้ป่วยตอบสนองต่อการรับ FFP 20 มล./กก. ต่อด้วย 10 มล./กก. ทุก 12 ชั่วโมง 3 วันติดต่อกันและ prothrombin complex concentrate 500 ยูนิตวันละครั้งอีก 3 วัน เมื่อมาติดตามการรักษา 2 สัปดาห์ต่อมา ปรากฏว่าผู้ป่วยไม่มีอาการเลือดออก ผลการตรวจทางห้องปฏิบัติการเป็นปกติทั้งหมด ระดับโปรทรอมบิน 94%, anticardiolipin antibody เป็นผลลบ และสารต้านต่อโปรทรอมบินเป็นผลลบ ผู้นิพนธ์ได้ศึกษาจีนที่ควบคุมการสร้างโปรทรอมบิน พบ single nucleotide polymorphism 9 ตำแหน่ง ซึ่งเป็นการค้นพบใหม่ 2 ตำแหน่ง (4096T→C, 4097 T→C) ส่วนอีก 7 ตำแหน่งนั้นเหมือนกับที่เคยรายงานในผู้ป่วยที่มีภาวะโปรทรอมบินต่ำแต่กำเนิด single nucleotide polymorphism เหล่านี้ไม่ใช่สาเหตุของโรค และไม่ได้บอกว่ามีความผิดปกติของจีนที่ควบคุมการสร้างโปรทรอมบินที่เคยมีรายงานในผู้ป่วยที่มีภาวะโปรทรอมบินต่ำแต่กำเนิด*
สรุป: *ภาวะเลือดออกในผู้ป่วยรายนี้เกิดจากภาวะโปรทรอมบินต่ำเป็นภาวะที่เกิดขึ้นภายหลังเนื่องจาก antiphospholipid antibody ที่เกิดขึ้นชั่วคราว ซึ่งตอบสนองต่อการให้ FFP และ prothrombin complex concentrate*