

## Neonatal Purpura Fulminans Due to Homozygous Protein C Deficiency

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Homozygous protein C (PC) deficiency is a rare hereditary disorder of blood coagulation resulting in microvascular and venous thromboses, usually purpura fulminans (PF), starting shortly after birth. If untreated, the coagulopathy and the skin lesions progress and finally result in death. We describe the case of a female neonate with homozygous PC deficiency and PF. The patient had rapidly progressive purpuric skin lesions and a very low PC level which was consistent with homozygous deficiency. She was treated successfully with fresh frozen plasma (FFP) and warfarin without apparent complications. Homozygous PC deficiency is a fatal disorder, but we were able to avoid the complication and save her life with early recognition and treatment. (*Ann Dermatol* 16(4) 176~179, 2004)

*Key Words:* Neonatal purpura fulminans, Protein C deficiency, Fresh frozen plasma, Warfarin

### INTRODUCTION

Purpura fulminans (PF) is a rapidly progressive syndrome that is characterized by widespread necrosis of the skin in the setting of disseminated intravascular coagulation (DIC). This syndrome may occur in 3 distinct situations: (1) in individuals with hereditary or acquired dysfunction of the protein C (PC) system or other coagulation regulatory mechanisms (hemostasis-initiated PF), (2) in individuals with acute and severe infection (acute infectious PF), and (3) in individuals without known acute infection or abnormalities of the coagulation regulatory mechanisms (idiopathic PF)<sup>1</sup>. PC is a plasma serine protease that has anticoagulant and profibrinolytic activities. Homozygous PC deficiency is usually associated with the development of severe

and often fatal PF and DIC during the neonatal period<sup>2-18</sup>. In 1983, Branson et al.<sup>18</sup> first described a newborn infant with PF and DIC secondary to a severe deficiency of PC. To our knowledge, only two cases of neonatal PF with homozygous PC deficiency have been reported in the Korean dermatological literature<sup>8,17</sup>. Herein we report a rare case of neonatal PF due to homozygous PC deficiency.

### CASE REPORT

A two-day-old female infant was transferred to our hospital because of rapidly progressive large purpuric lesions on the lower back, left buttock, and right thigh. She was born at term after an uncomplicated pregnancy of a 32-year-old mother. She was otherwise well and there was no history of postnatal trauma. Her parents and sibling were healthy and there was no family history of recurrent thromboses, bleeding disorders, and consanguinity.

Physical examination of the skin showed well-demarcated purpuric lesions with central necrosis on the lower back (1.5 × 1.0 cm), left buttock (2.0 × 1.5 cm), and right thigh (3.0 × 4.0 cm) (Fig. 1A, B). And bilateral corneal opacity was noted. Results of initial laboratory studies disclosed the following

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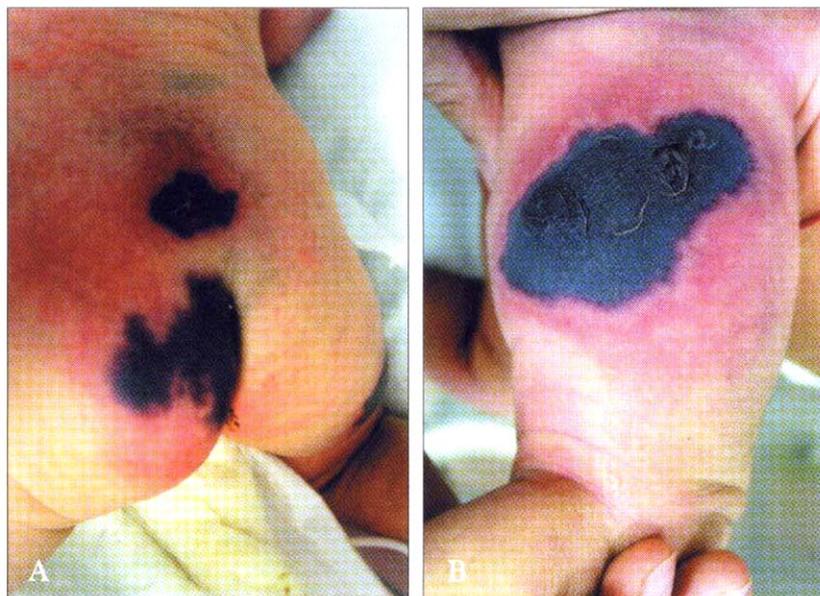


Fig. 1. Well-demarcated purpuric lesions with central necrosis are seen on the lower back, left buttock (A), and right thigh (B).

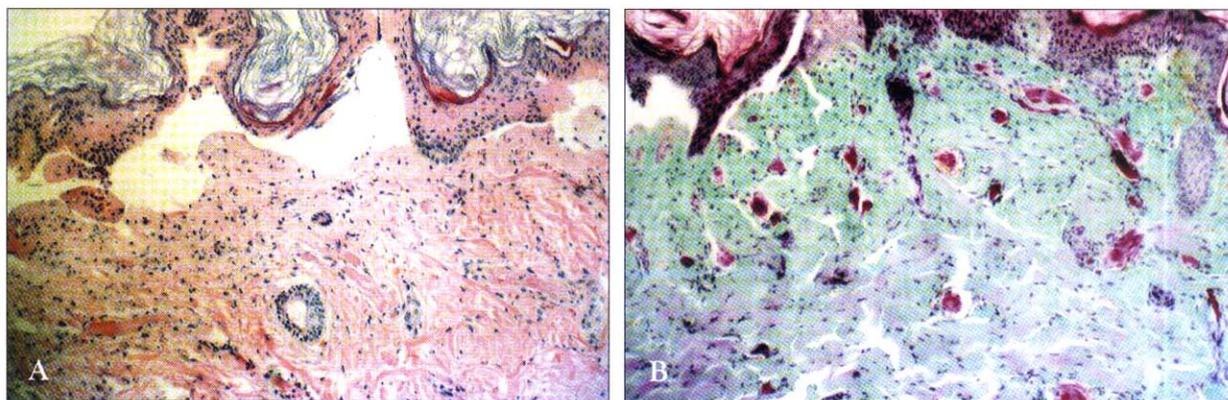


Fig. 2. (A) A skin biopsy specimen shows epidermal necrosis, fibrin thrombi filling vessels, and perivascular hemorrhage (H&E,  $\times 200$ ). (B) The vessels are completely filled with fibrin thrombi (Lendrum,  $\times 200$ ).

values; hemoglobin 12.8 g/dl, hematocrit 37.2%, white blood cell count  $20.5 \times 10^3/\mu\text{l}$ , platelet count  $108 \times 10^3/\mu\text{l}$ , prothrombin time 14.3s, partial thromboplastin time 36.2s, fibrinogen 355 mg/dl, fibrin degradation products  $> 160 \mu\text{g/ml}$ , D-dimer  $> 6400 \text{ ng/ml}$ , which were consistent with those of DIC. Also, VDRL, lupus anticoagulant, antiphospholipid antibody, blood culture for septicemia, and serologic test for viral infection were negative. Urinalysis and chest X-ray were normal. Ophthalmologic examination found microphthalmia, shallow

anterior chamber, and bilateral central vitreal masses similar to that seen in persistent hyperplastic primary vitreous. A biopsy specimen taken from the right thigh showed epidermal necrosis, subepidermal bulla formation, and bland fibrin thrombi filling all vessels of the dermis associated with perivascular hemorrhage (Fig. 2A). Fibrin was demonstrated with Lendrum stain (Fig. 2B). The plasma level of PC antigen and its activity were determined for the proband, parents, and sibling (Table 1). As seen in Table 1, the proband had a very low PC level and

**Table 1.** Plasma Levels of Protein C and S for the Patient and Family Members

	Protein C		Protein S	
	Antigen (%)	Activity (%)	Antigen (%)	Activity (%)
Patient	< 12	10	28	88
Father	35	71	116	81
Mother	55	73	53	67
Sibling	34	63	67	72
Normal Value	72-160	73-142	60-150	60-140

thus was considered homozygous for PC deficiency. The sibling and both parents had PC levels below the normal level, defining them as heterozygotes. A diagnosis of PF due to homozygous PC deficiency was made, and replacement therapy with FFP was initiated with 15 ml/kg every 12 hours. Supplementation with normal FFP transfusions rapidly improved lesions already present and appeared to effectively prevent the formation of new ones. On the 6th day of treatment we commenced anticoagulant therapy with warfarin at a dose of 0.3 mg/kg/day orally. The dose of FFP was gradually tapered starting on the 12th day of treatment, and discontinued on the 24th day of treatment. At present, the patient is being maintained on a regimen of warfarin, and she is developmentally normal except for persistent blindness.

## DISCUSSION

Protein C, a vitamin K-dependent serine protease, is a potent anticoagulant that inhibits factors Va and VIIIa and stimulates fibrinolysis. PC deficiency can be either hereditary or acquired condition. Hereditary PC deficiency is inherited as autosomal with two modes, one a dominant form in which the heterozygotes have recurrent venous thromboembolism starting in young adulthood and the other a recessive form in which the heterozygotes are asymptomatic and the homozygotes develop the syndrome of PF in the neonatal period as in our case<sup>2-18</sup>.

Homozygous PC deficiency is a rare genetic disease with fatal PF occurring during the neonatal period. The skin lesions have appeared essentially on all parts of the body, with the majority occurring on

the extremities, buttocks, abdomen, and scalp. Lesions may also develop at pressure points and also at sites of previous punctures. The areas become dark red and purplish black with bullae, then necrotic and gangrenous. In addition cerebral complications such as hemorrhagic or thrombotic infarction and hydrocephalus, and ophthalmic manifestations such as vitreous hemorrhage, retinal detachment, microphthalmia, shallow anterior chamber, and finding similar to persistent hyperplastic primary vitreous have been reported<sup>2,4,7,9,11,19</sup>. For confirmation of homozygous PC deficiency, the infant should have undetectable PC activity and both parents should be heterozygous for PC deficiency. In our case the patient had very low protein C antigen and activity levels, and the parents and sibling had subnormal levels. In addition the laboratory findings should be consistent with DIC and the histopathologic appearance is characterized by epidermal necrosis, focal perivascular hemorrhage, and occlusion of dermal arterioles, capillaries, and veins by microthrombi. A variety of histochemical stains such as phosphotungstic acid hematoxylin (PTAH), periodic acid-Schiff (PAS), and Lendrum can be used to aid in the identification of fibrin material<sup>20</sup>. Although numerous therapeutic modalities have been used, the optimal therapy for patients with homozygous PC deficiency remains in question. The current recommended treatment protocol is to use FFP infusion for initial treatment and warfarin for long-term treatment<sup>2-12</sup>. Although the use of PC concentrate is a good alternative<sup>13,14</sup>, it has many problems, including loss of venous access and catheter-tip thrombosis. Other therapeutic options include the use of low-molecular weight heparin<sup>5,6,16</sup>, antithrombin III<sup>15</sup>, factor IX concentrates, steroids, and liver transplantation. Homozygous PC deficiency

is a fatal disorder, but one in which early recognition of the clinical syndrome and appropriate intervention may be lifesaving. Our report describes a case of neonatal PF due to homozygous PC deficiency that has been treated successfully with FFP and warfarin.

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