A Case of Neonatal Purpura Fulminans Due to Homozygous Protein C Deficiency

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Homozygous Protein C deficiency is a rare genetic disease with catastrophic and fatal purpura fulminans like or thrombotic complication occurring during the neonaral period. Purpura fulminans is characterized by microvascular thrombosis in the dermis followed by perivascular hemorrhage, necrosis, and minimal inflammation. Laboratory findings are consistent with disseminated intravascular coagulopathy. We report a case of purpura fulminans in a neonate with the findings of disseminated intravascular coagulopathy and an undetectable level of protein C activity, whose parents proved to be heterozygous protein C deficiency. (Ann Dermatol 6:(1) 63~68, 1994)

Key Words: Homozygous Protein C Deficiency, Purpura Fulminans

Purpura fulminans is a very rare and catastrophic disease occurring in neonates and children[1-5]. It is at least in part a cutaneous manifestation of syndrome of disseminated intravascular coagulation (DIC) characterized by microvascular thrombosis in the dermis and subsequent perivascular hemorrhage and necrosis[1-7]. Clinical features include the sudden appearance of a large ecchymotic area, fever, shock and DIC with corresponding hematological data[1-4,8].

It usually follows some acute infectious disease such as scarlet fever, varicella, streptococcal pharyngitis or meningococcal meningitis in children[3,8]. However purpura fulminans in neonate can occur in patients with hereditary protein C deficiency without antecedent infections[1-3,9-13].

Protein C, when activated, is a vitamin K-dependent serine protease that functions as a natural anticoagulant and profibrinolytic molecule and plays a crucial role in regulating hemostasis[6,14]. Homozygous protein C deficiency if inherited as an autosomal dominant trait[14,15]. It usually manifests itself by purpura fulminans and, less commonly, by massive large vein thrombosis, and there is evidence of intrauterine thrombosis[6,7].

REPORT OF A CASE

A 3 day-old Korean female infant was referred to our department because of rapidly developed large ecchymoses on the buttocks and lower abdomen after delivery. She was delivered at 37 week gestation by caesarean section. At birth, her weight was 4,000gm and her general condition was good. There was no family history of diabetes mellitus, bleeding disorders, blood dysrlasia, thromboembolic phenomenon, and consanguinity. Her parents and one sibling were reported to be well.

Received February 1, 1993
Accepted for publication August 12, 1993
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This case was presented at the 44th Annual Meeting of the Korean Dermatological Association on April, 18, 1992.

Table 1. Plasma Level of Protein C Activity and Antigen for the Patient and Family Members.

	Activity(%)	Protein C Antigen(%)
Normal range	70-130	70-130
Patient	< 10	ND
father	28	76
Mother	43	50
Sibling	100	148

ND: not determined

On the day of admission, her vital signs were normal. Physical examination revealed the skin lesion with well demarcated central purpuric zone with erythematous halo over both sides of the flanks(7×6cm, 3×2.5cm) and buttocks (5×5cm, 5×5cm) (Fig. 1). The remainder of the physical examination was unremarkable.

Results of initial laboratory studies disclosed the following values; red blood cell count; 4.72× 10^6/mm^3, hemoglobin; 17.0gm/dl, white blood cell count; 14,000/mm^3, with 0.7 polymorphonuclear leukocyte, 0.2 lymphocyte, platelet count; 132, 000/mm^3,reticulocyte; 1.3%, erythrocyte sedimentation rate; 20mm/hr. The values for electrolytes, liver function test, and renal function test were normal. Blood culture for septicemia and serologic test for viral infection were negative. Chest and abdominal roentgenograms were reported as normal.

On hospital day 2, the hemoglobin and platelet count decreased to 13.1gm/dl and 73,000/mm^3, respectively. LDH and bilirubin increased to 543 IU/dl and 11.0gm/dl, respectively. Other hematologic findings (direct and indirect Combs' test, prothrombin time, partial thromboplastin time, serum fibrinogen degradation product) and urine fibrinogen degradation product were normal or negative.

On hospital day 8, the laboratory data showed prolonged prothrombin time(38. 1sec.) and partial thromboplastin time (171. 1sec.), a significant increase in fibrinogen degradation product of urine (1:4) and plasma (1:8), anemia and thrombocytopenia, which were consistent with those of DIC. The plasma levels of protein C antigen and its activity were determined for the proband, parents, and sibling (Table 1). As seen in table 1, the proband had a complete lack of detectable protein C and thus was considered homozygous for protein C deficiency. But the parents had protein C concentrations below 60% of normal value, defining them as heterozygotes.

A biopsy of the affected skin performed on the second hospital day showed epidermal necrosis, subepidermal bulla formation, and thrombosis of dermal and subcutaneous blood vessels (Fig. 2, 3).

Over the hospital days the lesions were tending to be symmetrically distributed on the abdominal wall, buttocks, and extremities. A typical lesion began as a well-defined blanchable erythematous macule and developed into a central purpuric zone with a gunmetal-gray or purpuric appearance. Most lesions persisted and became indurated. The central purpuric zone then became necrotic and bled as the black eschar retracted from the surrounding viable skin(Fig.4). On the hospital day 8, dry gangrene developed on both hand sand progressed rapidly. At that time her general condition was aggravated. Despite intravenous infusion of heparin and fresh frozen plasma, she expired on the 10th hospital day.

DISCUSSION

Protein C is a vitamin K-dependent plasma glycoprotein with a molecular weight of 62,000 daltons[6,13] that has been mapped on chromosome [2.15] It is synthesized by the liver as a zymogen and has a plasma half-life of 8.1 hours[6,13]. Activated protein C has potent anticoagulant and profibrinolytic activities[6,13]. Protein C activation is catalyzed when thrombin first forms a complex with the endothelial cell surface receptor protein, thrombomodulin[13,16]. Protein C activity is regulated by a specific plasma protein inhibitor[13,17].

Protein Ca acts as an anticoagulant by selective-

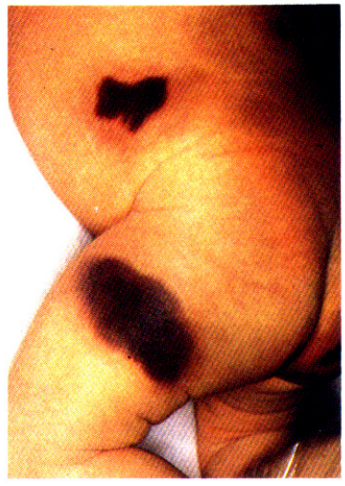

Fig. 1. Typical appearance of lesion on the 3rd hospital day: well demarcated central purpuric zone with erythematous halo on the left thigh.

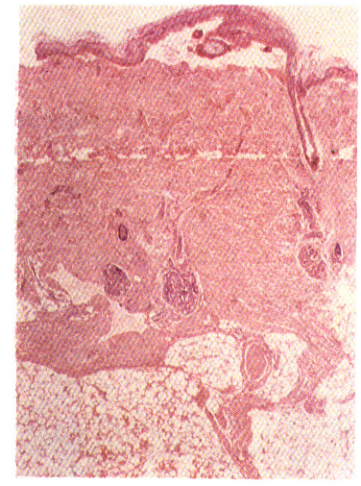

Fig. 2. Skin biopsy specimen of purpuric zone shows epidermal necrosis, subepidermal bulla formation, and thrombosis of entire dermal blood vessels (H & E, × 40).

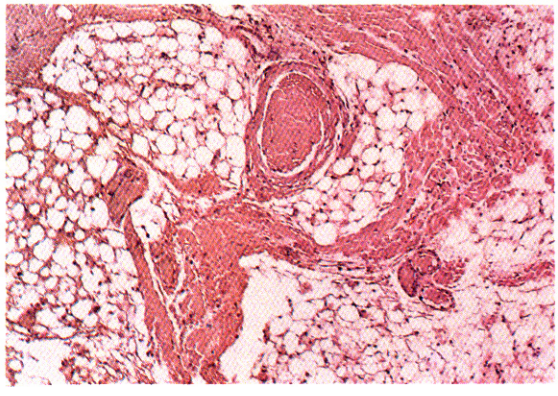

Fig. 3. Skin biopsy specimen shows fibrin thrombi filling all subcutaneous blood vessels (H & E, × 40).

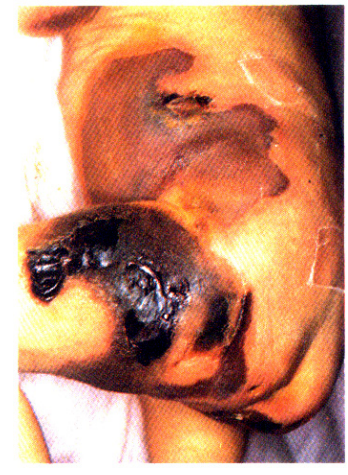

Fig. 4. More extended skin lesion with central necrosis and eschar formation on the 8th hospital day.

ly inactivating the procoagulant factor V and VIII[6,13]. The proteolytic deqradation of factor V and VIII is enhanced another vitamin K-dependent cofactor, Protein S[6,13]. Protein C induced its fibrinolytic action by neutralizing a circulating inhibitor of tissue plasminogen activator(t-PA)[13,18]. This increases t-PA activity, which promotes the conversion of plasminogen to plasmin and facilitates thrombolysis. Thus the absence of protein C's regulatory function and degradation factor V and VIII results in an increased incidence of thrombotic diseases[13,14].

Protein C deficiency can be a hereditary or acquired condition. Hereditary deficiency of protein C, whether heterozygous or homozygous, typically has an autosomal mode of inheritance. The heterozygous state is associated with the potential for the development of deep venous thrombosis or pulmonary embolus starting in late adolescence or early adulthood. The level of protein C in the heterozygous patient is typically 30% to 65% of that found in a normal individual. Homozygous protein C deficiency, with an estimated incidence of one in every 500,000 to 750,000 births, is not compatible with life if left untreated. Affected infants develop purpura fulminans and DIC within the first 48 hours of life. Protein C activity levels in these patients are below the lower limit of detection(usually less than 3%). Both parents are heterozygous for the trait, and there is often a his-

tory of consanguinity[12,19]. In the present case, the patient had a complete lack of detectable protein C level and this was considered as homozygous protein C deficiency. But the parents had protein C concentrations below 60% of normal value, being defined as heterozygotes.

To data there have been 20 cases of homozygous protein C deficiency in the United States and Europe[19,21], with all but one case resulting in purpura fulminans[22]. The one homozygous protein C-deficient infant without purpura fulminans had significant thrombosis in the inferior vena cava, both renal veins, and both iliac veins. In Korea, this is the first reported case of homozygous protein C deficiency with purpura fulminans. The skin lesions typically begin as well-defined ecchymoses that may in eschar formation with full thickness ulceration[9-11]. The extent and severity of skin involvement is variable; some lesions may resolve spontaneously without scarring[10,12]. Any site can be involved, but there is a tendency for symmetrical distribution[9-12] and occurrence at sites of trauma[12]. Dehydration, prolonged exposure to cold, and other factors that may promote stasis have been associated with the development of purpuric lesion.[11,12] In the present case, the skin lesions began as large ecchymoses on both buttocks and abdomen at 17 hours of age. Over the hospital days the lesions were tending to be symmetrically distributed on the abdominal wall, buttocks, and extremities and began to form eschar. But there was no evidence of any extrinsic factors that promote stasis.

The occurrence of thrombosis in the microcirculation is a unique feature of severe protein C deficiency. Although massive venous thromboembolism is a rare initial manifestation of this disorder,[22] thrombotic complications inevitably cause death if untreated[3,22]. Widespread venous thrombosis may occur. Cavernous sinus involvement may result in hydrocephalus, seizures, and intracerebral hemorrhage[3,9,22]. Eye changes include micro-ophthalmia, cataracts, and retinal detachment secondary to hemorrhage with blindness[3,9,10]. Anemia can follow gastrointestinal and genitourinary tract involvement with thrombosis and hemorrhagic infarcts of mucosal surfaces[9,22]. Deep vein thrombosis, renal vein thrombosis with infarction of the kidneys, and pulmonary embolism have also been described[9,22].

During the acute phase of purpura fulminans, the laboratory results are consistent with DIC, including decreased platelets, decreased fibrinogen, increased fibrin split products, and prolonged prothrombin and partial thromboplastin time.[12,22] The protein C activity level is undetectable. During asymptomatic periods, the other vitamin K-dependent factors and all other coagulation factors are within the normal range for children of a similar age. In the majority of cases, both parents proved to be heterozygous for protein C deficiency without clinical manifestations of thrombotic diseases[6,7]. In the present case, the patient had laboratory findings of DIC with a lower level of protein C activity, and both parents were heterozygous for protein C deficiency.

Biopsy specimens from the affected skin revealed microthrombi in nearly all the capillaries and small vessels. Older lesions showed epidermal necrosis with occasional bullae formation and extensive hemorrhage into the subcutaneous fat.[9,11] Our biopsy specimen showed epidermal necrosis, subepidermal vesicular formation, and thrombosis of dermal and subcutanceous blood vessels.

Purpura fulminans can also be present as part of an acquired syndrome developing as a sequela to a nonspecific infection and associated with DIC[4,8]. This rare disorder, seen mostly in the winter and spring, occurs predominantly in children, but may rarely affect adults[4]. Purpura fulminans often appears after a latent period of four weeks (range, 0 to 90 days) following preparatory, usually infectious illnesses that may include scarlet fever, streptococcal bacteremia, varicella, or viral-induced upper respiratory tract infection.[4,8] Fever, hypotension, and purpura fulminans make up the three clinical features of the syndrome.[4] The characteristic skin lesions appear during the first three days of the disease process and are identical to those seen in homozygous protein C deficiency.[4,8] The clinical situations associated with protein C deficiency are neonatal purpura fulminans, resulting from a hereditary homozygous protein C deficiency; Coumarin necrosis, from a hereditary heterozygous protein C deficiency; and DIC, meningococcal-associated purpura fulminans, and lupus anticoagulant syndrome, associated with an acquired protein C deficiency. Coumarin necrosis is a rare condition in which purpura fulminans is associated with a severe protein C deficiency induced by oral anticoagulant therapy. The pro-

posed mechanism of coumarin necrosis in protein C deficiency is as follow; with the onset of the anticoagulant therapy, the level of protein C decreased rapidly, relative to the other vit K-dependent factors(II, IX, X) with longer half lives. This creates a temporary imbalance in which the procoagulants predominate and permits the local thrombosis of vessels seen in coumarin necrosis[23-27]. Deficiency of protein S has also been associated with purpura fulminans. protein S, another vit K-dependent protein, is a cofactor for active protein C; it complexes with activated protein C on phospholipid vesicles and causes a tenfold increases in protein C's inactivation of factor Va. Deficiency of protein S has also been associated with thrombosis.[28]

For the confirmation of homozygous protein C deficiency in a neonate with purpura fulminans or massive venous thrombosis, the infant should have the findings of DIC with undetectable protein C activity, and both parents should be heterozygous for protein C deficiency.[29] But, the definitive diagnosis of homozygous protein C deficiency is difficult in the neonate.[1,2] In a normal newborn infant, the concentrations of vitamin K-dependent coagulation factors, including protein C, are reduced in comparison with adult levels.[29,30] Therefore, during DIC in the newborn infant, protein C level may be undetectable even in the absence of a hereditary defect. Whenever homozygous protein C deficiency is suspected, protein C level should be measured, not only in the neonate but also in the parents and siblings, so that the hereditary nature of the deficiency can be confirmed. Relating the level of protein C to those of another vit K-dependent protein synthesized by the liver distinguishes inherited protein C deficiency from protein C deficiency due to secondary causes, such as liver diseases or vit K deficiency, in which all vit K-dependent factors are depressed. In the present case, the levels of protein S and other vit K-dependent factors were not measured. But the patient had the laboratory findings of DIC with undetectable level of protein C activity, and both parents were heterozygous for protein C deficiency. These findings led this case to be diagnosed as a neonatal purpura fulminans due to homozyous protein C deficiency.

At the onset of the symptoms, the initial treatment should be plasma (8 to 12 ml/kg every 12 hours) untill all lesions have healed[2,12]. Two modalities for longterm treatment are acceptable as useful in these children: oral anticoagulant therapy or protein C replacement (fresh frozen plasma or prothrombin complex concentrate)[10,11,12]. Oral anticoagulant (vit K antagonist, maintaining the prothrombin time from one and one-half to two times control values or at the International Normalized Ratio of 2.5 to 4.4) is the choice for long-term treatment[2]. Heparin, dipyridamole, and aspirin have shown to be ineffective in controlling the disease[10,11,12].

We have now described an infant who developed clinical, histologic, and hematologic sings of purpura fulminans due to homozygous protein C deficiency shortly after birth without any evidence of the involvement of extrinsic pathogens known to trigger intravascular coagulation.

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