Purpura Fulminans with Transient Protein C and Protein S Deficiency

Geçici Protein C ve Protein S Eksikliğine Bağlı Purpura Fulminans

Güldane Koturoğlu, Fadıl Vardar, Cihangir Özkınay, M.Tayyip Aslan, Hüseyin Onay, Kaan Kavaklı, Zafer Kurugöl, Ferda Özkınay.
Ege University, Faculty of Medicine Department of Pediatrics, *Izmir, Turkey*

Summary

Purpura Fulminans is a rare but devastating disease. The acute infectious type is the commonly encountered form of the disease and is responsible for about 90% of the cases. The most common etiologic factors are *Neisseria Menengitidis* and β hemolytic Streptococcus among bacterial agents, and Varicella Zoster among viral infections.

We present the case of a previously healthy 2.5-year-old boy with hemorrhagic skin lesions characteristic of purpura fulminans. Laboratory analyses revealed very low protein S and C levels. Blood culture revealed *Staphylococcus aureus*. The patient received daily replacement therapy with fresh frozen plasma for 15 days and anticoagulation with low-molecular-weight heparin for 15 days. In addition, he received Teikoplanine therapy. Despite generous plasma infusions, skin necrosis progressed rapidly into compartment syndrome which required fasciotomy and skin grafting. Protein S and Protein C remained low for 3 months despite treatment.

We presented this case in order to emphasize that *S. aureus* should be considered among the etiologic agents of post-infectious secondary purpura fulminans, and the treatment should be considered accordingly. *(J Pediatr Inf 2008; 3: 124-6)*

Key words: Purpura Fulminans, *Staphylococcus aureus*, Protein S, Protein C

Özet

Purpura fulminans nadir görülmesine karşın oldukça kötü prognozlu bir hastalıktır. Akut enfeksiyöz tipi yaygındır ve olguların yaklaşık %90'ından sorumludur. Etyolojik nedenlerden en sıklıkla sorumlu olan ajanlar *Neisseria meningitidis,* β-hemolitik streptokoklar ve varisella zoster virus enfeksiyonudur.

İki buçuk yaşında erkek olgu kliniğimize hemorajik deri lezyonları ile başvurdu. Laboratuar incelemelerinde protein S ve protein C seviyeleri çok düşük saptandı. Kan kültüründe *Staphylococcus aureus* üredi. Olguya Teikoplanin ve netilmisin tedavisi verildi. Aynı zamanda koagülasyon dengesini sağlamak üzere heparinize edildi ve taze donmuş plazma tansfüzyonu yapıldı. Ancak bu tedaviye rağmen deri lezyonları hızla ilerledi ve kompartman sendromu gelişti. Protein S ve Protein C seviyeleri 3. ayda normal sınırlara geldi.

Bu olgu sunumu ile enfeksiyona sekonder purpura fulminans nedenleri arasında *Staphylococus aureus*'un da düşünülmesi gerektiği ve tedavi seçiminde bu mikroorganizmanın da gözönünde bulundurulması gerektiği vurgulanmıştır. *(Çocuk Enf Derg 2008; 3: 124-6)*

Anahtar kelimeler: Purpura fulminans, *Staphylococus aureus*, Protein S, Protein C

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Yazışma Adresi
Correspondence Address
Dr. Güldane Koturoğlu
Ege Üniversitesi Tıp Fakültesi Çocuk Sağlığı ve Hastalıkları, 35100
Bornova, İzmir
Gsm: +90 505 653 53 51
E-mail:
guldane.koturoglu@ege.edu.tr

Introduction

Rare thrombotic events during childhood usually take place due to deficiency of some factors inhibiting coagulation like Protein C (PC), Protein S (PS), and antithrombin III (1). Protein S and Protein C are synthesized from liver in the presence of vitamin K. Protein S and Protein C levels are lower than normal levels during first 6 months of life. Homozygous PC deficiency result in serious thrombotic complications during neonatal period while heterozygous PC and PS deficiency may come to clinical attention due to recurrent thrombotic events till 15 years old age (2). Transient PC and PS deficiency has been described in various pathologic conditions related with purpura fulmi-

nans. Especially, PC and PS levels were found to decrease significantly compared with antithrombin III during severe bacterial infections with *Neisseria meningitidis* (3). However, the reason for this decrease is not well-known. In addition, PS level is found to decrease more than level of other factors in purpura fulminans secondary to varicella and streptococcus infection and this decrease was found to be due to auto-antibodies against PS.

This case is presented to emphasize that transient PS and PC deficiencies may occur during Stapylococcus infections and *Staphylococcus Aureus* should also be considered as an etiologic factor of purpura fulminans.

Case Report

2.5 years old boy was admitted to Ege University Hospital with the complaints of purple colored lesions over the right hand, flexor part of right and left wrist, and right and left calves. His past medical history revealed that he had upper respiratory tract infection 15 days ago. Parents, consanquineous, were healthy, especially without any history of thromboembolism.

On admission, physical examination revealed weight of 13 kg (10- 25 percentile), height of 90 cm (10-25 percentile), heart rate 120/minute, respiratory rate 36/minute and body temperature 38ºC. Hemorrhagic bullous gangrenous area was present over the right hand and 1/3 distal part of right forearm. There was crusted lesion 2x2 cm in size with surrounding diffuse ecchymotic area. Besides, there was a 10x15 cm sized ecchymotic area over the right calf. Otherwise he was normal.

Laboratory evaluation revealed a hemoglobin level of 6,5 gr/dl, hematocrit of 18%, MCV 71.3 fl, leukocyte count of 17.700/mm^3, platelet count of 69.000/mm^3, sedimentation rate 40 mm/hr and C- reactive protein 2.4 md/dl. Peripheral blood smear showed 80% polymorphonuclear leukocyte (PNL), 20% lymphocyte, erythrocytes were hypochrome and demonstrating microcytosis, poikilocytosis and anisocytosis. Reticulocyte count was 5%. Prothrombin time was 16 second, activated partial thromboplastin time was 29.5 second, fibrinojen level was 155,6 mg/dL and D-Dimer was found to be positive.

The patient was considered to have disseminated intravascular coagulation (DIC) because he had ecchymottic and petechial lesions and oozing from these lesion sites, thrombocytopenia and positive D-Dimer. He was heparinized and given fresh frozen plasma as well as whole blood. Differential diagnosis of DIC included microangiopathic pathologies like infectious reasons (purpura fulminans), soft tissue injury due to trauma, snake or insect venom, severe thrombotic, thrombocytopenic purpura and hemolytic uremic syndrome and hereditary thrombotic abnormalities like anthithrombin lll deficiency, and heterozygous PC and PS deficiency. Culture of the lesions and blood culture were obtained for probable infectious agents resulting in purpura fulminans. Lumbar puncture was carried out to obtain cerebrospinal fluid and asses for central nervous system infection. Central nervous system infection was not detected. However, since the patient had leukocytosis, elevated CRP level and a left shift at the peripheral smear cefuroxim, neutromycine and metronidazole were initiated. Since the radial pulse was not palpable, orthopedics and vascular surgery consultations were carried out. Emergency fasciotomy was performed due to compartment syndrome in the right forearm.

Snake and insect bites were not considered to be responsible from purpura fulminans due to history and physical findings.

We investigated our patient and his parents for probable hereditary thrombotic diseases by measuring PC, PS and antithrombin levels. In addition, genetic analysis for Factor V Leiden and Prothrombin mutations was performed.

Blood culture of the patient grew *Staphylococcus aureus* and the antimicrobial treatment was changed as Teikoplanine to cover the etiologic microorganism. Antithrombin level of the patient was found to be 80.1%. However, PC and PS levels were both found to be low (Table l).

Protein S and Protein C levels of the parents were within normal limits. Factor V Leiden and Prothrombin mutations were not observed. We considered post infectious purpura fulminans secondary to PC and PS deficiency. Teikoplanine was stopped at the 30th day of the treatment. Heparin treatment and fresh frozen plasma infusion were stopped at the 15th day. Graft was placed to the fasciotomy site of the right forearm at the 8th week. Follow up of the patient at the end of the 3rd month of treatment, the patient was found to be totally normal and laboratory investigations revealed normal levels of PC and PS.

Discussion

This patient was considered to have disseminated intravascular coagulation (DIC) because he had ecchymottic and petechial lesions and oozing from these lesion sites, thrombocytopenia and positive D-Dimer. Differential diagnosis of DIC included microangiopathic pathologies like infectious reasons (purpura fulminans), soft tissue injury due to trauma, snake or insect venom, severe thrombotic, thrombocytopenic purpura and hemolytic uremic syndrome and hereditary thrombotic abnormalities like antithrombin lll deficiency, and heterozygous PC and PS deficiency. Except transient purpura fulminans all other diseases were excluded with history, physical examination and laboratory findings. Purpura fulminans is rare but a devastating disease.

Tablo 1. Protein C and Protein S Levels of the patient.

	Acute Attack	End of the 1st moth	End of the 3rd month
Protein C	60.36%	69.87%	82.44%
Protein S	1%	25.75%	105.2%

Acute infectius type is more frequent and is responsible from approximately 90% of cases. Though it is seen commonly secondary due to *Neisseria meningitidis* infection, other gram (-) bacteria and gram (+) bacteria like group A β-hemolytic Streptococcus may also result in purpura fulminans. Besides, it may also occur due to viral infections, mostly due to Varicella infection. It has been shown that PS and PC levels decrease transiently secondary to auto antibodies formed during post infectious purpura fulminans (1-8). Although auto antibodies were not shown in our case, PC especially PS deficiency might due to auto antibodies.

Purpura Fulminans, secondary to *S. aureus* has been reported to be rare. Rintala et al. has reported just a case of PF case secondary to *S. aureus* out of 12 case series of PF patients (8). In Kravitz et al.' s paper in which 5 cases were discussed, superantigens produced by S.aureus were shown to be responsible for purpura fulminans (7).

The main treatment principle of PF is to restore the coagulation balance and to terminate the underlying etiologic cause. For this reason, heparin is commonly employed. Smith et al. used PC concentrates in post infectious PF and reported significant increases in serum level of PC (1). Besides, it has also been reported that plasmapharesis in these patients result in significant elevations in PC levels. Since Ig G type auto antibodies have been in PF with infectious origin, it has been planned to decrease blocking activity by intravenous immune globulin (6). We have detected satisfactory regression in extremity necrosis in our patient with appropriate antibiotherapy as well as low molecular weight heparin. We repeated PC and PS serum levels test and found normal limits at the 3rd month after treatment.

In conclusion, although acute post infectious PF is frequently after *N. Menengitidis* and β hemolytic streptococcus infections, our case developed PF after *Staphylococcus aureus* infection. For this reason, we suggest that *Staphylococcus aureus* should be considered in differential diagnosis of post infectious PF.

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