A case of purpura fulminans secondary to transient protein C deficiency as a complication of chickenpox infection

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SUMMARY: Canpolat C, Bakır M. A case purpura fulminans secondary to transient protein C deficiency as a complication of chickenpox infection. Turk J Pediatr 2002; 44: 148-151.

Purpura fulminans is a rare but dramatic disease which occurs most commonly during or after an infection. It is characterized by extensive involvement of the skin and extremities and involvement of visceral organs. Purpura fulminans, when occurring after a viral infection such as varicella, is usually characterized by purpuric lesions involving the trunk, usually with sparing of the visceral organs. In this report we describe a child with purpura fulminans due to a transient protein C deficiency as a complication of chickenpox infection.

A seven-year-old girl developed bruise-like lesions on her extremities on the fifth day after eruption of varicella exanthem. She had no previous history of bleeding tendency or thrombosis. Family history was also negative. On the seventh day of her illness she was admitted to Marmara University Hospital with widespread echymotic an partially crusted chickenpox lesions. CBC, urinalysis and blood chemistries were within normal limits. She had a prolonged aPT and apt with low serum fibrinogen and high D-dimers suggestive disseminated intravascular coagulation (DIC). Protein C activity was low. Punch skin biopsy was consistent with purpura fulminans. She was treated with heparin and fresh frozen plasma which helped her to recover clinically as well as hematologically. She was discharged with still low protein C activity that returned to normal by the next follow-up visit.

Key words: purpura fulminans, protein C deficiency, chickenpox.

Purpura fulminans (PF) is a descriptive term depicting a heterogeneous group of disorders characterized by rapidly progressive purpuric lesions, which may develop into extensive areas of skin necrosis and peripheral gangrene[1]. The disorder is associated with laboratory evidence of consumptive coagulopathy. The histopathologic features are widespread thrombosis of the dermal capillaries and venules with hemorrhagic infarction of the surrounding tissues[1,2]. The condition is often fatal, and survivors may have considerable morbidity related to loss of digits, limbs or areas of skin[3].

Purpura fulminans occurs most commonly in three different clinical settings. Transient or congenital deficiencies of protein S or protein C have been documented in cases of purpura fulminans in recent years[4]. The most common association is with sepsis with microorganisms such as Staphylococcus aureus[5], groups A and B beta hemolytic streptococci[6], Streptococcus pneumoniae[7], and Hemophilus influenzae[8]. It also is considered a cardinal feature of meningococcal septicemia[9]. The second groups of patients with PF are neonates and infants with inherited deficiencies of protein C and protein S. Recognition of these rare patients has drawn attention to the role of protein C anticoagulant pathway in the genesis of dermal vascular thrombosis[4]. The third group of patients includes those with PF that occurs a few days to weeks after the onset of a febrile illness[3,10]. Numerous infections have been reported to precede this disorder, the most common being varicella and streptococcal infections, which occur in 30% and 20% of patients, respectively[3]. The onset of the PF during the convalescent phase of the preceding febrile illness suggests that the disorder may be immunologically mediated. The overall mortality rate reported before 1964 was more than 50%[2]. In

more recent reports, the average mortality rate was 18% (14% in children)[3]. A wide range of therapies has been used, including clotting factor replacement[11], vitamin K[12], glucocorticosteroids[2,12], epsilon aminocaproic acid[13], hyperbaric oxygen[14], heparin[7,15], dextran[16], and exchange tranasfusion[17].

Case Report

A previously healthy seven-year-old girl developed pain in her knees on the fifth day after eruption of varicella exanthem. The pain was associated with bruise-like lesions on both her knees which was said to have spread to her thighs within 24 hours. She had been treated with acetaminophen for fever from the first to the fourth day of her exanthem. She had no previous history of excessive bleeding, easy bruisability or thromboses and no previous hospitalizations or serious illnesses. She also had no history of varicella infection or vaccine. There was no family history of bleeding disorder or thromboses.

On the seventh day of illness, when she was admitted to Marmara University Hospital for further evaluation, the physical examination showed an alert and oriented girl with normal vital signs for her age. She had widespread echymotic lesions on both sides of her knees and left thigh. The lesions were irregular in shape with well-demarcated borders and a surrounding rim of erythema. There was also widespread, partially crusted papulovesicular skin lesions typical for chickenpox (Fig. 1).

Her hemoglobin was 13.2 g/dl and hematocrit 40%. Platelet count was 186,000/mm^3 and the white blood cell (WBC) count was 16,200/mm^3 with differential of 60% segmented neutrophils, 35% lymphocytes, and 5% monocytes. Urinalysis was normal. Liver and kidney function tests as well as serum protein levels were within normal limits.

Her prothrombin time was 18.3 seconds with INR of 1.45, activated partial thromboplastin time 69.7 seconds, and fibrinogen 80 mg/dl (range: 180-350 mg/dl). Plasma levels of factors V, VII, IX and XI were normal. D-dimer test was positive at 1: 36,335. Protein C activity was 41.7% (70-140%) and protein S activity was 67.7% (60-130%) at the second day of admission. Lupus anticoagulant and anticardiolipin antibody tests were negative and antivaricella IgM and IgG were positive. Protein C activity of the patient

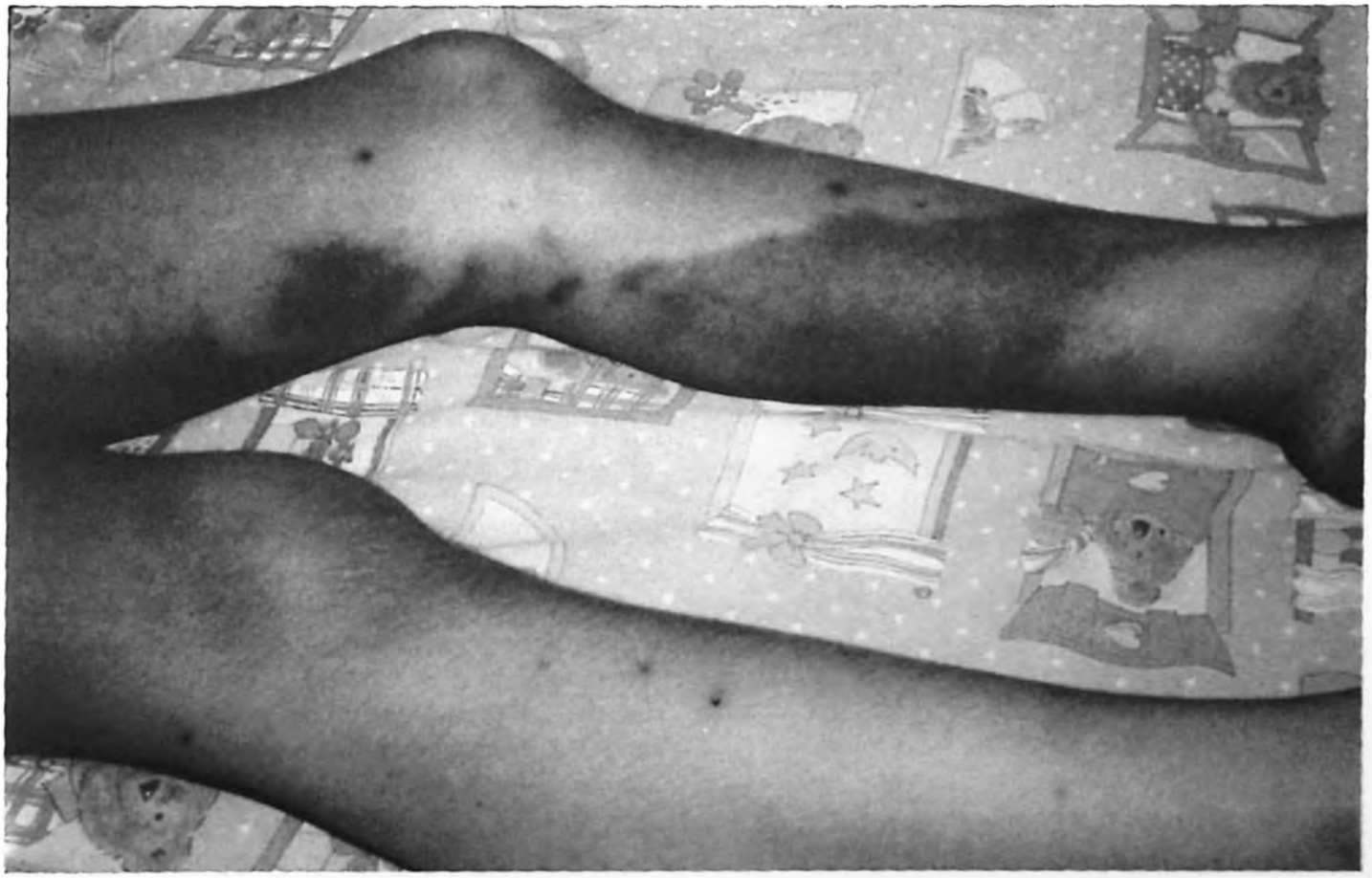

Fig. 1. Purpuric lesions involving medial sides of left knee and leg with typical papulovesicular skinlesions seen in chickenpox.

remained low after 1:1 mixing study with normal plasma. Protein C and protein S levels of the patient's parents and the first-degree relatives were within normal limits. Punch skin biopsy of the margin of the left thigh lesion showed numerous fibrin thrombi, without accompanying vasculitis, and epidermal and dermal necrosis consistent with purpura fulminans.

On the day of admission, she was started on continuous infusion of unfractionated heparin (100 U/hr) and received multiple 10 ml/kg of fresh frozen plasma infusions. During her hospital course, she had full correction of her prothrombin time, partial thromboplastin time, fibrinogen, and D-dimer test, but her protein C activity remained low. She remained afebrile and her skin lesions regressed. She was discharged from the hospital 13 days after admission with oral warfarin. Follow-up clinic visits showed full normalization of her purpuric lesions and correction of the protein C activity.

Discussion

Protein C is the best known among the identified anticoagulant factors in the delicate molecular balance of hemostasis. Activated protein C degrades activated coagulation factors VIIIa and Va, attenuating their procoagulant activation of factors X and prothrombin. Protein S, a vitamin K-dependent glycoprotein, functions as a nonenzymatic cofactor of activated protein C[18], accelerating the inactivation of factors VIIIa and Va, which accounts for the increased risk of thrombosis associated with protein S deficiency states[19]. Depletion of both protein C and protein S has been reported to occur in patients with septicemia-associated purpura fulminans[19,20]. In these cases laboratory evidence of consumptive coagulopathy was also present. It is not known whether low levels of protein C or protein S following such infections are of primary importance in inducing PF or are secondary to consumption coagulopathy caused by other mechanisms.

Although protein C may be depleted as part of disseminated intravascular coagulopathy[21], protein C levels in our patient remained low throughout her admission in the presence of normal levels of protein S and vitamin K-dependent clotting factors VII and IX, and normalizing levels of fibrinogen and D-dimer. Thus protein C deficiency was apparently central to the pathogenesis of the disease. Protein C and protein S levels in the first generation family members of the patient were normal. This, together with the transient nature of the protein C deficiency, excludes familial protein C deficiency as the cause of her disorder.

In 1993, D'Angelo[27] first described the association between transient protein S deficiency and circulating autoantibodies directed against protein S. These anti-protein C or anti-protein S type autoantibodies are IgM and IgG type and they persist for only a few months, after which time the activities of the proteins return to normal. The autoantibody appears to act by binding to and increasing the clearance of protein C or protein S. The frequency with which antibodies to protein C or protein S are induced in children with varicella infection is unknown. Because of the unavailability of the antibody tests in the hospital and outside laboratories, we were not able to confirm the presence of anti-protein C antibody, but we believe that the levels of protein C remaining low after 1:1 mixing test suggests its presence. .

Anticardiolipin antibodies have been associated with quantitative protein S deficiency[23] and functional impairment of protein C anticoagulant pathway[24]. An elevated IgG anticardiolipin antibody titer was also documented in the patient described by D'Angelo et al[22]. Because the titers were not consistently elevated, their contribution to the pathogenesis of the thromboemboli event was difficult to determine. In our patient, we failed to demonstrate any lupus anticoagulant or anticardiolipin antibodies.

It has not been clear whether post infectious PF is mediated by an inflammatory or a vasculitic process, by platelet microthrombi, or by activation of coagulation pathways. As a result, a wide range of therapies has been used. Recognition that the disorder is predominantly a thrombotic process resulting from the deficiency of antithrombotic factors suggests that immediate heparinization is the preferred treatment. Likewise, we believe that administration of heparin, together with large volumes of fresh frozen plasma, terminated the progression of the disease in our patient. Protein C concentrate has been used successfully in the treatment of purpura fulminans associated with disseminated intravascular coagulation and severe acquired protein C deficiency[25].

Based on the available case series of varicella-associated PF in children, it appears reasonable to evaluate children with any varicella-associated

thrombotic event for the presence of protein C or protein S deficiencies. Screening for lupus anticoagulant for anticardiolipin antibodies might also be considered. It should also be stressed that most PF cases secondary to varicella were associated with protein S deficiency rather than protein C deficiency[26,27]. This association of protein C deficiency with PF is, we believe, an interesting point of our case.

The rare but potentially serious occurrences of thrombotic events associated with varicella infection further support recommendations for universal vaccination of children for varicella.

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