

Varicella-associated Purpura Fulminans and Multiple Deep Vein Thromboses: A Case Report

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Abstract

Varicella-associated purpura fulminans is a rare syndrome associated with substantial morbidity and mortality. General supportive care, heparinization, and plasma infusions are the mainstays of treatment. A patient aged 8 years and 8 months with purpura fulminans and multiple deep vein thromboses after varicella infection because of deficiencies of proteins C and S is presented in this case report.

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Key words: varicella, purpura fulminans, thrombosis, protein C, protein S

Introduction

Varicella-associated purpura fulminans (PF) is a rare syndrome associated with substantial morbidity and mortality. It is characteristically associated with autoimmune protein S deficiency and profound hypofibrinogenemia^{1,2}. A patient aged 8 years and 8 months with PF and multiple deep vein thromboses after varicella infection due to deficiencies of protein C and protein S is presented in this case report.

Case Report

A boy aged 8 years and 8 months was brought to our emergency department because of pain, swelling, and bruising of his legs on the sixth day after eruption of varicella exanthema (**Fig. 1**). The next day purpuric, petechial lesions began to develop on the left thigh, and a 5 × 2-cm bullous



Fig. 1 Purpura on the lower extremity

lesion began to develop on the right thigh. Then, both lower limbs, especially the left, became swollen, and the pain began to increase. The patient had no history of bleeding disorders, hospitalization, or serious illnesses. He had not had varicella infection or received varicella vaccine. There was no family history of bleeding disorders. His weight and height

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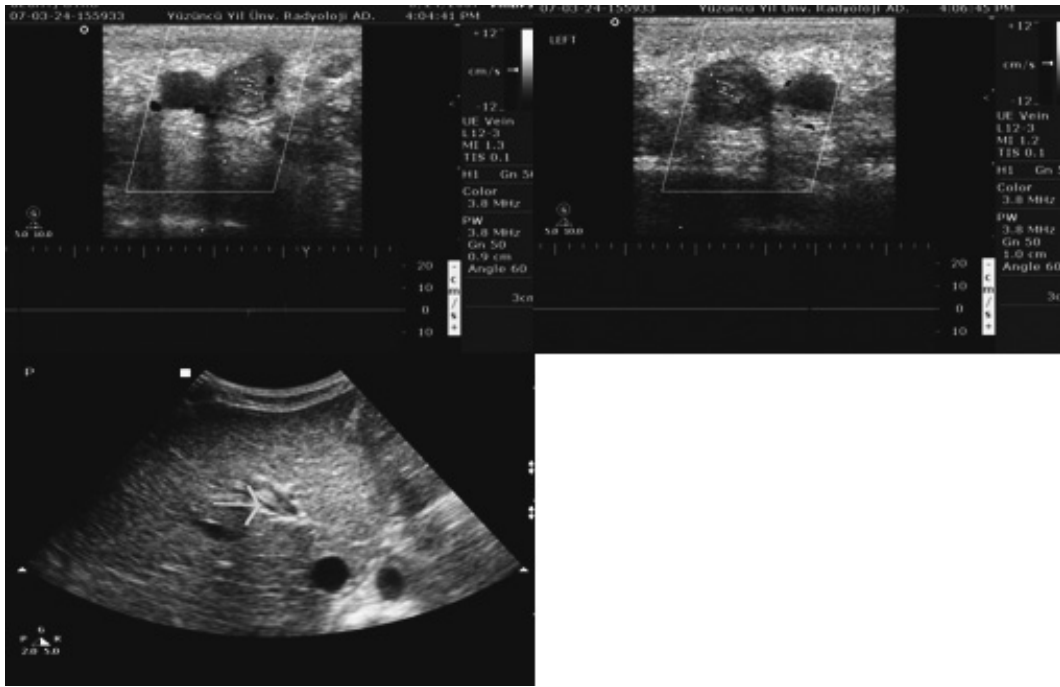


Fig. 2 Thrombosis of the left lower extremity, prominent thrombosis of the right lower extremity, and partial thrombosis of the left branch of the left portal vein

were 24 kg (10th to 25th percentile) and 140 cm (90th to 97th percentile), respectively. His temperature was 36.5°C, the heart rate was 88 beats/minute, the respiratory rate was 20 breaths/minute, and the blood pressure was 100/70 mmHg. Both femoral pulses were palpable, and scabbed varicella lesions were present. The purpuric lesions were located on the lateral areas of both legs. A necrotic, dark purple lesion, 7 × 2 cm in size, with an irregular but distinct rim of erythema was present over the posterior aspect of the left leg. The entire left leg was excessively swollen, painful, and cyanotic. The hemoglobin concentration was 10.3 g/dL, and the hematocrit was 30.9%. The platelet count was $13.9 \times 10^9 L^{-1}$, and the white blood cell count was $14.8 \times 10^9 L^{-1}$ with a differential of 56% segmented neutrophils and 44% lymphocytes. The results of liver and renal function tests and serum electrolyte levels were within the normal ranges. The prothrombin time, activated partial thromboplastin time, and fibrinogen level were 19.5 seconds (normal range: 11–14 seconds), 34 seconds (normal range: 31–40 seconds), and 41 mg/dL (normal range: 175–400 mg/dL), respectively. The results of the D-Dimer test were 51 µg/mL (normal range: <0.5 µg/mL). Levels of factors V, VII, VIII, and XII, and antithrombin III were normal. Serologic tests for lupus anticoagulants, antinuclear antibody, and

anticardiolipin antibody IgG and IgM serologies were negative. Nevertheless, protein C levels were 20% (normal range: 70%–130%), and protein S levels (normal range: 60%–140%) were undetectable. Results of Doppler ultrasonography examination of the lower extremities were normal. Postvaricella PF was diagnosed, and low molecular weight heparin (nadroparin, 100 U/kg/12 hours, subcutaneous) (LMWH) was administered along with fresh frozen plasma (FFP) infusion (10 cc/kg/day). While the bullous, bruising lesions and skin eruption were resolving, the right leg became swollen on 12th hospital day. Doppler ultrasonographic analysis revealed thrombosis of the right common femoral vein, the superficial femoral vein, and the popliteal vein. The blood flow was not determined in these veins. Results of an examination of the veins of the left leg were normal. Treatment with classic heparin (mean dose: 140 U/kg/hour) was started instead of treatment with LMWH, and the FFP dose was increased to 30 cc/kg/day because of rapid disease progression. The dose of classic heparin was determined on the basis of activated partial thromboplastin time. Methyl prednisolone (30 mg/kg/day) was added to the treatment. Intravenous concentrates of immunoglobulin and protein C were not available, so they were not given. Plasma exchange could not be performed because of

Table 1 Shows the clinical progress and treatment changes on following

| Treatment day | Clinical Progress | PT | aPTT | Fibrinogen | D-dimer | Protein C | Protein S | Treatment |
|---------------|---|---------------|---------------|--------------------|------------------|---------------|---------------|---|
| | | N: 11 – 14 sn | N: 31 – 40 sn | N: 175 – 200 mg/dL | N: 0 – 0.5 µg/dL | N: 70 – 130 % | N: 60 – 140 % | |
| 1 | PF | 19.5 | 34.0 | 41 | 51 | 20 | <10 | LMWH 100 U/kg/12 hours, FFP infusion (10 cc/kg/day) |
| 12* | The right common femoral vein, superficial femoral vein and popliteal vein thrombosis | 16.6 | 24.2 | 66 | 44 | 29 | 20 | Classic heparin (100–150 U/kg/hour; mean dose, 140 U/kg/hour) , FFP (30 cc/kg/day) , methyl prednisolone (30 mg/kg/day) |
| 18 | Thrombosis of the left lower extremity and prominent thrombosis of the right lower extremity, partial thrombosis of the left branch of the left portal vein and right iliac vein, total thrombosis of the left iliac vein | 19.9 | 229.4 | 209 | 17 | 30 | 115 | Classic heparin (100–150 U/kg/hour; mean dose, 140 U/kg/hour) FFP (30 cc/kg/day), methyl prednisolone (20 mg/kg/day) |
| 23** | | 20.5 | 30.2 | 266 | 5.0 | 25 | 90 | LMWH (100 U/kg/12 hours) , FFP infusion (30 cc/kg/day), methyl prednisolone (10 mg/kg/day) |
| 30 | | 13 | 30.3 | 244 | 1.05 | 25 | 73 | LMWH, 100 U/kg/12 hours, methyl prednisolone (2 mg/kg/day) |
| 90 | No thrombosis | 13.7 | 30 | 306 | 0.4 | 28 | 70 | LMWH, 100 U/kg/12 hours |

PT: prothrombin time, aPTT: activated partial thromboplastin time

technical problems. When the thrombosis of the right lower extremity was resolving, abdominal pain with marked superficial abdominal skin veins and swelling of left lower extremity with pain were detected 4 days after the thrombosis of the veins of the right lower extremity. Therefore, Doppler ultrasonographic analysis was performed again. In addition to prominent thrombosis of the veins of the right lower extremity, thrombosis of the veins of the left lower extremity, partial thrombosis of the left branch of the left portal vein and the right iliac vein, and total thrombosis of the left iliac vein were detected (**Fig. 2**). Owing to clinic improvement, the treatment was not changed. On the 26th hospital day, while protein S levels were increasing, no increase in protein C levels was detected. The dosage of methyl prednisolone was 30 mg/kg/day once a day for 1 week and was then decreased to 20 mg/kg once a day for 1 week. Finally, the methyl prednisolone

dosage was decreased to 10 mg/kg/day once a day for 1 week and to 2 mg/kg once a day for 1 week. Infusions of FFP (30 cc/kg/day) were given for 1 month. Treatment with LMWH, instead of classic heparin, was begun on the 23rd hospital day. After 2 months, the thrombosis resolved, and protein S levels were in the normal range, but protein C levels remained low (**Table 1**).

Discussion

PF is an acute, rapidly progressive hemorrhagic necrosis of the skin attributable to dermal vascular necrosis which is associated with disseminated intravascular coagulation³. Postinfectious PF usually occurs 7 to 10 days after onset of symptoms of acute infection¹⁴⁻⁷. The ecchymotic lesions are most commonly distributed symmetrically on the lower extremities and buttocks. Visceral involvement is

less frequent⁸. Our patients' symptoms had begun 7 to 10 days after varicella and involved the lower extremities, as in previously recorded cases.

Transient or congenital deficiencies of protein C or S have been documented in many cases of PF in recent years^{4,7}. Transient deficiency of protein S activity has been described as a potential causal factor in the development of varicella-associated PF. The mechanism of transient protein S activity associated with varicella infection appears to be the induction of anti-protein S immunoglobulin M and immunoglobulin G autoantibodies. These antibodies persist for only a few months, after which time the protein S activity returns to normal¹. The initial deficiency of protein C activity is rapidly corrected with treatment. Our patient had low levels of protein C and protein S, as in previously reported cases. While protein S levels recovered on the 26th day of treatment, unlike in previously reported cases, protein C levels remained low. Therefore, congenital protein C deficiency was diagnosed.

Because PF and deep vein thrombosis are primarily thrombotic processes, prompt heparinization is indicated. Heparinization should be combined with aggressive blood product replacement using cryoprecipitates and concentrates of protein C and antithrombin to replace factors consumed⁹. FFP infusions usually fail to restore protein S levels, and no protein S concentrate is available². Plasma exchange allows the infusion of large volumes of plasma, while reducing the titer of the protein S autoantibodies, in conjunction with steroid therapy². If progressive life- or limb-threatening thrombosis occurs despite these measures, then fibrinolytic therapy should be considered. Anticoagulation therapy should be continued until the free protein S levels return to normal². In our case, varicella-associated PF, deep vein thrombosis, and autoimmune protein S deficiency was thought (UNCLEAR) on diagnosis, and LMWH therapy was started. Nevertheless, the subsequent failure of LMWH treatment was thought to be due to the increase in thrombotic events. Therefore, classic heparin treatment was chosen instead of LMWH. In previously reported cases, treatment failure has been attributed to a low dose of LMWH. In addition to classic heparin treatment, high-dose FFP infusion was performed instead of

plasma exchange. With the aim of preventing production of autoantibodies against protein S, treatment with methyl prednisolone was started. In most reported cases, methyl prednisolone has been given at a dosage of 10 mg/kg/day. However, a consensus about the methyl prednisolone dosage is still lacking. Therefore, we used a methyl prednisolone dosage of 30 mg/kg/day. Our patient had congenital protein C deficiency and acquired protein S deficiency. An evaluation of previously reported cases and the present case support the hypothesis that 2 or more concurrent abnormalities in the naturally occurring anticoagulant pathway are necessary to trigger the development of PF during varicella infection³.

In conclusion, we have observed that, in conditions for which protein C concentrates are not available not and plasma exchange cannot not be performed, methyl prednisolone, FFP, and classic heparin should be used at higher doses for the effective treatment of varicella-associated deep vein thrombosis and PF.

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