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Letter to the Editor

Successful Treatment of Diffuse Alveolar Hemorrhage with Recombinant Factor VIIa in a Child with Henoch-Schönlein Purpura

Henoch-Schönlein Purpurası Olan bir Çocukta Diffüz Alveoler Hemorajinin Rekombinan Faktör VIIa ile Başarılı Tedavisi

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Henoch-Schönlein Purpura (HSP) is a multi-system small vessel vasculitis that commonly manifests with palpable purpura along with acute arthritis, gastrointestinal involvement, and glomerulonephritis.[1] Neurological, pulmonary, cardiac, and genitourinary complications rarely occur. Mortality and morbidity related to HSP is usually due to severe gastrointestinal and renal involvement. Pulmonary hemorrhage with fatal respiratory failure has seldom been reported.[2-6] In life-threatening bleeding situations, even without pre-existing coagulopathies, recombinant factor VIIa (rFVIIa) seems to be a possible choice for treatment. The primary mode of action used by rFVIIa to stop the bleeding focuses on the tissue factor (TF)-dependent coagulation activity, which also affects the activated platelet surface.[7-11]

We report a case of life-threatening diffuse pulmonary hemorrhage due to HSP in which acute fatal bleeding was successfully stopped with rFVIIa, despite the fact that the patient had no preexisting coagulopathy.

An 11-year-old-girl presented with a purpuric rash on the extensor surface of her lower and upper limbs and complained of wrist and ankle joint pain. In the second day of her hospitalization, she began having abdominal pain and passed bloody stools. She was treated with oral prednisolone 1 mg/kg twice a day. At presentation, her examination showed a weight of 31 kg, normal vital signs, blood pressure of 100/60 mmHg, and the purpuric rash on the extensor surface of her lower and upper limbs. Her right wrist and right ankle joints were slightly swollen with some limitation of movement, but the rest of her examination was normal. There was no history of any autoimmune disease in her family, and she was not suffering from another autoimmune disease herself.

Laboratory tests showed hemoglobin 14.8 g/dl, platelets 370x109/l, white blood cells (WBC) 15.6x109/l, normal range prothrombin time (14 s) and activated partial thromboplastin time (36 s), serum sodium 140 mmol/l, potassium 3.8 mmol/l, blood urea nitrogen 7.6 mg/dl, and creatinine 0.56 mg/dl (which increased

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to 0.93 mg/dl after three days). The complement protein C3 was 1.3 g/l, and the C4 was 0.36 g/l. The antinuclear antibody, anti-DNA, and antineutrophil cytoplasmic antibody (ANCA) along with the viral markers were all negative. Urinalysis showed negative protein, red blood cells >5 per/high-power field (HPF), and WBC 8-10 per/HPF. On day three, she suddenly developed significant respiratory distress and required immediate intubation and ventilation. At the same time, hematuria and proteinuria began. Her hemoglobin level dropped to 9.6 gr/dl in a six-hour period. Despite intense mechanical ventilation support, the hypoxia did not resolve. Massive bleeding continued through the endotracheal tube, and erythrocyte suspension were urgently administered. Because of the serious hypoxia, we decided to administer rFVIIa to stop the bleeding. Recombinant FVIIa (NovoSeven®, Novo Nordisk, Copenhagen, Denmark) was initiated at a dose of 30 μg/kg every six hours. After the fourth dose of rFVIIa, the bleeding stopped. She remained on the ventilator for seven days and was then extubated. A percutaneous kidney biopsy of 35 glomeruli performed at the 10th day of her hospitalization revealed minimal cellular proliferation without any crescents, and immunofluorescence studies showed minimal immunoglobulin A (IgA) staining without C3 along with immunoglobin M (IgM) and immunoglobin G (IgG). Initially, she was started on oral prednisolone treatment, but when her proteinuria increased to 150 mg/m^2/h and massive pulmonary bleeding started, she was changed to pulse therapy with methyl prednisolone (30 mg/kg per dose on alternate days for three doses) and cyclophosphamide (500 mg/m^2). When discharged after one month of hospitalization, her serum creatinine was 0.6 mg/dl, and the urine protein was 22 mg/m^2/h with moderate blood. Her blood pressure increased when her pulmonary bleeding started, but it was controlled with nifedipine and enalapril. The patient received monthly doses of cyclophosphamide (500 mg/m^2 i.v) for three months and received prednisolone (16 mg) on alternate days, and she continued to do well. After three months, the cyclophosphamide was stopped, and azothioprine was started and continued for six months. Nine months later, her serum creatinine had dropped to 0.5 mg/dl, and her urine was negative for protein but still weakly positive for blood. The prednisolone and azothioprine treatment were gradually discontinued, and her blood pressure remained normal. When seen in the clinic one year later, her blood pressure was normal, she was off all medications, and her urine was free of protein and blood.

Diffuse alveolar hemorrhage (DAH) is a rare but serious pulmonary complication that occurs in HSP. Mortality is very high in those who require mechanical ventilator support. When we reviewed the English literature, we came across only a few case reports concerning DAH in HSP.[2-6] Therapy with steroids alone is usually not enough to control this kind of severe bleeding; however, a treatment which combines pulse steroids and cyclophosphamide seems to be effective. Despite these kinds of efficient drugs, some extra time is required to observe their effects.

In severe cases, some other treatment options are needed to immediately control the bleeding. For all cases of acute onset DAH, therapeutic approaches should focus on the emergent stabilization of the patient and the suppression of active disease. Supportive care includes treating the hypoxemia, perhaps even with mechanical ventilation. Positive end-expiratory pressure during mechanical ventilation might produce a tamponade effect to stop vascular bleeding. In situations of hemodynamic instability and severe hemorrhage, packed red blood cell transfusions may be required.

In our case, despite applying the measures above, we could not control the bleeding, and severe hypoxemia continued for several hours. Therefore, we administered four doses of rFVIIa, at a dosage of 30 μg/kg every six hours, and after the fourth dose of rFVIIa, the bleeding stopped. Her hypoxemia resolved, and her hemoglobin increased. Luckily, we controlled the massive bleeding without any side-effects at a lower dose than is normally recommended.

The standard recommended dose of rFVIIa can be used at 35-70 μg/kg per dose every two-three hours.[7]

An effective and successful life-saving, symptomatic therapy involving parenteral or intrapulmonary administration of rFVIIa to stop life-threatening critical bleeding has been reported in only a few patients with DAH.[8-11] However, whether local rFVIIa treatment is safe remains controversial. Therefore, we applied rFVIIa via the parenteral route, and the acute bleeding was successfully controlled.

This case illustrates the successful use of rFVIIa in an HSP patient with DAH. We especially want to emphasize that rFVIIa can be used successfully with life-threatening DAH. Emergent control of the bleeding helps save time until the other drugs can take effect.

Declaration of conflicting interests

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