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PLASMA EXCHANGE IN REFRACTORY AUTOIMMUNE ANEMIA IN A CHILD WITH SYSTEMIC VASCULITIS ASSOCIATED WITH HOMOZYGOTE BETA THALASSEMIA*

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A four-year-old girl presenting with fever and purpuric lesions was diagnosed with systemic vasculitis based on her clinical and laboratory findings. She also had homozygote beta thalassemia. Oral steroids were administered and during the course of her treatment she developed necrotizing lesions on her extremities along with severe myalgia and an autoimmune refractory anemia. Autoantibodies against the Rh antigen causing a persistent hemolysis of her erythrocytes were detected in her serum. Since no improvement in her skin lesions and autoimmune hemolytic anemia was achieved with bolus methylprednisolone therapy and cyclophosphamide, plasma exchange was performed. After three sessions of plasma exchange, her immune complex and autoantibody levels gradually declined and a remission in her clinical and laboratory findings was achieved. We suggest the use of plasma exchange along with conventional therapy for similar cases with ongoing immunologic injury. *Key words: refractory autoimmune anemia, plasma exchange, autoantibodies, vasculitis.*

In most cases of vasculitis there is indirect evidence of immune complex disease, although the inciting antigen (Ag) is often not found[1,2]. In various types of vasculitis, autoantibodies may be involved in these immune complexes with an abnormal imbalance and interaction of viral, genetic and immunologic factors[3]. The presence of circulating serum autoantibodies with no organ specificity may also be expected. Plasma exchange is an effective way of reducing the amounts of circulating antibody and/or immune complexes in patients with antibody-mediated or immune complex-mediated disease[2,4]. We present a four-year-old

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patient with systemic vasculitis in whom we attempted to modify the primary disease and clear the autoantibodies against Rh system (D) Ag by plasma exchange therapy.

Case Report

This four-year-old girl was admitted to our hospital with persistent fever in the previous few months and recent maculo-papular eruptions. She had been hospitalized for fever in a local hospital. She also complained of swelling and pain in the dorsum of the right hand and arthritis in the lower extremities. Her parents were first cousins. The first child of the family had received multiple blood transfusions for his thalassemia and had died at the age of two years. One other sibling was healthy and six years old.

Physical examination on admission revealed a pale child with palpable purpuric lesions and livedo reticularis over the extremities and abdomen. Her body temperature was 38.5°C, pulse rate 156/min, and blood pressure 100/50 mmHg. The liver and spleen were enlarged by 5 cm and 4 cm, respectively. She had severe myalgia in the lower extremities with arthritis of the knees.

Laboratory examination revealed the following: hemoglobin 6.35 g/dl, hct 18%, WBC count 18,000/mm^3, and thrombocyte count 272,000/mm^3. The blood smear showed anisocytosis, poikilocytosis, hypochromia and microcytosis. Reticulocyte count was 6.6%. Her blood type was 0 Rh+. Direct Coombs test was positive and anti-complement Coombs test was negative. Plasma Hb level was 26.3% and haptoglobulin was 0. Hemoglobin electrophoresis was compatible with homozygote beta thalassemia: HbA2 2.4%, HbF 76%; starch electrophoresis A+, F4+, A2 normal; agar electrophoresis A+, F4+. Urine examination was normal. The renal and liver function tests were within normal limits. Creatinine phosphokinase was 79 u (N: 20-191). Complement 3(C3) and C4 levels were 50 mg/dl (N: 60-120) and 18 mg/dl (N: 20-55), immune complexes were 275 ug/ml (high), and the CH50 level was within normal limits. Antinuclear antibodies and anti-DNA titers were negative. Immunoglobulin levels were all increased. The electromyography and the muscle ultrasonography were compatible with myopathy/polymyositis.

During the hospital course, severe myalgia and fever dominated the patient's clinical course. Marked digital ulcerations and pain characteristic of polyarteritis nodosa (PAN) developed on the first and second fingers of the right hand. Cutaneous lesions consistent with vasculitis and the accompanying systemic findings were interpreted to be related to a vasculitis syndrome. Soon after steroid treatment was initiated at a dose of 2 mg/kg/day, improvement of symptoms was noted and the patient was discharged with a diagnosis of systemic vasculitis.

Six weeks later the steroid dosage was reduced. One week later the patient was readmitted with high fever, rash, cough and severe abdominal pain. On physical examination her body temperature was 40°C and she had bronchopneumonia and arthritis in the left distal interphalangeal joints. She again had a Coombs (+) hemolytic anemia, and occult blood was detected in her stool. Antineutrophil cytoplasmic antibodies (ANCA) (diffuse staining) were detected by indirect immunofluorescence.

Antibiotics were administered for her pneumonia. Although the pneumonia resolved with antibiotics, her fever persisted and a gradual decline was observed in the hemoglobin level. Bone marrow aspiration was normal. Autoantibody detected in the serum and eluate showed anti-D (Rho) specificity at a titer of 1/32. Necrotizing purpuric lesions recurred. A combined treatment including pulse methylprednisolone therapy at a dose of 30 mg/kg/day +cyclophosphamide 2.5 mg/kg/day +dipyridamole 3 mg/kg was initiated. However, the patient's anemia progressed, necessitating multiple blood transfusions in a single day, with no improvement in the severe symptoms nor in serological findings. Plasma exchange was hence performed. Double-filtration plasma exchange was carried out using a cellulose diacetate hollow fiber. Fresh frozen plasma was used as substitute plasma. The blood was circulated from the internal shunt at a rate of 40 ml/min, and the replacement plasma was substituted at one-fifth that rate (8-10 ml/min). After the first sesson, the autoantibody titer against Rh decreased to 1/8 and the Hb level remained stable for 72 hours. On the fourth day the Hb level again decreased to 3 g/dl, and the autoantibody level was again elevated to 1/32. Two additional sessions of plasma exchange were performed with an interval of three days. Oral low-dose steroid and cyclophosphamide were also continued. At the end of this treatment period, the autoantibody level declined, the Hb level was stabilized and there was a decline in the immune complex level. Clinically the patient's myalgia and skin lesions resolved. The family then migrated to another country.

Discussion

Systemic vasculitis is an immune-complex-mediated and/or autoantibody-mediated disease[3,4]. Therapeutic approaches consist mainly of high-dose corticosteroid and a number of cytotoxic drugs. A diagnosis of systemic vasculitis was accepted in the presented patient given the clinical and serological findings along with the positive ANCA result. Since it is believed that circulating ANCAs may contribute to the injurious effects of infiltrating leukocytes in the tissue, the beneficial effect of plasma exchange is obvious in the acute stages when the ANCA titer is high[5].

Retrospective studies on patients with vasculitis have shown improved survival

with administration of the combination of steroids plus cyclophosphamide or azathioprine[1]. The addition of intravenous methylprednisolone, methotrexate or plasma exchange to conventional immunotherapy (high-dose steroids and cytotoxic drugs) has also been reported to have some beneficial results[1,2,5]. Whether the combination of these drugs with plasma exchange therapy is of additional benefit is currently being evaluated in various clinical settings[4,5]. The rationale for the use of plasma exchange in vasculitis is that antibodies and mediators that cause the vascular damage by deposition in the arteriolar walls can be thus removed[5,6]. Plasma exchange should be considered in cases with rapidly progressing vascular disease with evidence of ongoing immune complex process[1]. Turner et al.[2] reported excellent results in seven of their eight patients with severe refractory cutaneous vasculitis. The indication for plasma exchange is also strengthened in cases like ours with detrimental effects of an autoantibody which cannot be controlled by conventional immunotherapy. Bernstein et al.[6] also reported a beneficial effect with plasma exchange in an idiopathic case of refractory acute autoimmune hemolytic anemia. Our case manifested an autoantibody against Rh antigen causing the hemolysis of erythrocytes. To our knowledge this is the first report of such autoantibodies in a systemic vasculitis case. The association of vasculitis with thalassemia major has not been previously reported either.

Since plasma exchange may induce a rebound of antibody formation which may exacerbate the disease, a combination of cytotoxic drugs is recommended to reduce this rebound effect[1]. We also applied this approach. After three sessions of plasma exchange, we achieved a consistent decrease in the autoantibody and immune complex titer and were able to arrest the hemolytic process in the patient. A regression in the symptoms of vasculitis was also observed. On the other hand, in renal vasculitis the results of plasma exchange therapy are reported to be less promising[4]. Overall, however, the association of plasma exchange with conventional immunotherapy has significantly reduced mortality in severe vasculitis[5]. This case report emphasizes the beneficial effect of this form of therapy in cases with ongoing immunologic injury indicated by immune complexes and autoantibodies.

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