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THE ROLE OF HIGH-DOSE METHYLPREDNISOLONE THERAPY IN PAROXYSMAL NOCTURNAL HEMOGLOBINURIA*

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Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired disorder characterized by intermittent hemolytic anemia. High-dose methylprednisolone (HDMP) was administered in two patients, eight- and 16-year-old females, with PNH. This drug produced a dramatic improvement in the hemoglobin level, leukocyte and platelet counts. No side effect was observed in either patient during the treatment period. The patients were followed up on an outpatient basis for six and 16 months. In conclusion, HDMP therapy for PNH appears to be more effective and safe than previously reported therapies. *Key words: high-dose methylprednisolone, paroxysmal nocturnal hemoglobinuria.*

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired, clonal hematologic disorder characterized by hemoglobinuria, thrombosis, infection and a tendency toward bone marrow aplasia[1].

The cause of hemolytic anemia seen in PNH is complement-mediated hemolysis[2]. Blood cells from patient with PNH contain an abnormal cell that lacks two complement regulatory proteins, Decay Accelerating Factor, (DAF) and CD59, both of which protect host cells from the action of complement. DAF and CD59 are phosphatidylinositolglycan (PIG)-anchored surface molecules[2,3]. The cause of PIG-anchored surface molecule deficiencies is defective synthesis of the molecules of glycosylphosphatidylinositol[4,5]. This mutant gene is termed PIG-A (phosphatidylinositol glycan class A)[5]. The localization of the PIG-A gene is found on p22.1 of the X-chromosome[5]. Therefore, pancytopenia may occur in patients with PNH[1,6].

Various treatment modalities, such as danazol, high-dose recombinant human erythropoietin (r-Hu EPO), corticosteroids and/or anabolic agents, and bone marrow transplantation have been used in PNH[1,7-11]. High-dose

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methylprednisolone (HDMP) was used in our two patients with PNH. Complete correction of hematological findings was observed in both patients following HDMP therapy.

Case Reports

Case 1

An eight-year-old girl came to the pediatric clinic with complaints of right hemiplegia and paleness for two days. She had a four-year history of recurrent jaundice, dark urine and paleness.

Physical examination revealed normal vital signs. Paleness, cutaneous petechiae, right hemiplegia and positive Babinski sign were found.

Laboratory examination: hemoglobin 6.4 g/dl; leukocyte 5,400/µl; mean corpuscular volume (MCV) 96.6 fl; thrombocyte 5,400/µl; reticulocytes 6%; differential count: 68% neutrophils, 24% lymphocytes, 8% band neutrophils and 2% normoblasts. Spherocytes were seen on peripheral smear. Direct Coombs was negative. Clotting time, prothrombin time, partial thromboplastin time, protein-C, protein-S, anti-thrombin-III, antinuclear antibody (ANA), anti DNA, C_3, C_4, antistreptolysin-O (ASO), osmotic fragility test, autohemolysis test and biochemical analyses were all within normal limits. Haptoglobulin was 16 g/dl and no microorganism was determined to grow in the throat culture. Lupus erythematosus (LE) cells were negative. Total bilirubin and direct bilirubin were 6.4 mg/dl and 0.8 mg/dl, respectively. Serum iron was 50 µg/dl, serum iron binding capacity 360 µg/dl and transferrin saturation 14%. Urine hemoglobin and acid-Ham test were positive. Hemoglobin electrophoresis was normal. Erythroid hyperplasia and hypocellularity were seen on the bone marrow smear. Multiple infarcts on the left parieto-occipital region were seen on cranial CT-scan.

High-dose methylprednisolone therapy was administered orally at doses of 30 mg/kg/day for three days, 20 mg/kg/day for four days, 10, 5, 2 mg/kg/d for one week, and 1 mg/kg/day according to hematological findings. Elevations in hemoglobin level (8.2-11.2 g/dl), leukocyte count (7,500-9,800/µl) and thrombocyte count (116,000-316,000/µl) were observed on the first and third weeks of treatment, respectively. Subcutaneous heparin therapy (50 u/kg/d) was supplemented. The patient has been followed on an outpatient basis for 16 months.

Case 2

A sixteen-year-old girl came to the pediatric clinic with complaints of vaginal bleeding, epistaxis and skin bruises for seven days. The patient had received a blood transfusion 25 days before coming to our clinic.

Physical examination revealed normal vital signs. Paleness, ecchymotic and purpuric lesions on her skin, epistaxis and vaginal bleeding were noted.

Laboratory examination: hemoglobin 8.2 g/dl, leukocytes 4,600/μl, thrombocytes 4,000/μl, MCV 71.3 fl, reticulocytes 6%, and differential count: 58% neutrophils, 40% lymphocytes and 2% monocytes. Anisocytosis was noted on the peripheral smear.

Biochemical analyses, direct Coombs test, partial thromboplastin time, prothrombin time, clotting time, ASO, C3, C4, ANA and anti-DNA were within normal limits, and LE-cells were negative. No microorganism was determined to grow in the throat swab culture. Total bilirubin and direct bilirubin were 4.3 mg/dl and 0.2 mg/dl, respectively. Serum iron was 34 μg/dl, serum iron binding capacity 335 μg/dl and transferrin saturation 10%. Haptoglobulin was 20 mg/dl, while the acid-Ham test and urine hemoglobin were positive. Erythroid hyperplasia was detected on the bone marrow smear.

High-dose methylprednisolone therapy was administered in a schedule similar to that in the previous case. Elevations in hemoglobin level (10.4-11.6 g/dl), leukoctyte count (7,400-10,200/μl) and thrombocyte count (64,000-230,000/μl) were observed in the first and third weeks of treatment, respectively. Ferrous iron (6 mg/kg/day) was also supplemented. The patient has been followed on an outpatient basis for six months.

Discussion

Paroxysmal nocturnal hemoglobinuria is now generally accepted as a disease in which bone-marrow-derived cells have deficient PIG-anchored surface molecules[2, 3]. Furthermore, Miyata et al.[5] suggested that these surface molecules are defective. DAF and CD59, which are PIG-anchored surface molecules, ameliorate the complement sensitivity of PNH red blood cell[12].

Paroxysmal nocturnal hemoglobinuria can arise from or evolve into aplastic anemia, sideroblastic anemia and myelofibrosis[11]. Iron-deficiency anemia may occur due to urinary loss of iron during intravascular hemolysis[13]. Iron-deficiency anemia also occurred in one of our patients (Case 2).

The precise mechanism of thrombosis in PNH is unknown. However, the platelets and leukocytes in patients with PNH are also abnormally sensitive to complement-mediated lysis. Certain aspects of complement-platelet interaction may predispose a patient to thrombosis[13]. Thrombosis was also been determined in one of our patients (Case 1).

Danazol has been used in patients with PNH. This drug has reportedly produced a dramatic improvement in hemoglobin levels and platelet counts, but was associated with a few androgenic side effects[7]. High dose r-Hu Epo for the treatment of anemia in two patients with PNH was administered. In one patient,

a relapse of severe aplastic anemia occurred and r-Hu Epo therapy was discontinued. Another patient showed too great an increase in hemoglobin, and monthly phlebotomies were done to reduce his iron overload. However, an increase in leukocytes and thrombocytes was not observed[8].

It has been suggested that glucocorticoid and androgen therapy is moderately effective in PNH. However, both are poorly tolerated, particularly by women[8, 14]. Marrow transplantation for aplastic complications of PNH has been found to be successful and well-tolerated. For patients without aplasia, the complication risk of transplantation as well as the life-threatening nature of thrombotic episodes and hemolysis have been reported[11].

Blood transfusions are valuable in the treatment of anemia, but they must be given in the form of saline-washed, or frozen-thawed, deglycerolized red cells. Transfusion of other preparations, especially fresh blood, may precipitate or accelerate the hemolytic process either by supplying components of complement or by inducing the formation of antibodies that activate early components of complement[15].

High-dose methylprednisolone therapy has succesfully been used in various hematologic disorders such as aplastic anemia, idiopathic thrombocytopenic purpura, myelofibrosis, acute leukemia and osteopetrosis instead of conventional prednisolone therapy[16].

HDMP therapy has been used previously in two adolescent patients with PNH[16]. In this study, HDMP therapy was administered to two adolescents with PNH. HDMP therapy has been observed to be successful and well-tolerated in patients with PNH. No side effects were noted during HDMP treatment. Patients' blood cells began to increase on the 7th day and reached normal levels on the 21st day of therapy. Recurrence was not seen in our patients within six and 16 months of HDMP therapy. Finally, we believe that PNH may be treated successfully with HDMP.

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