Successful management of severe chronic autoimmune hemolytic anemia with low dose cyclosporine and prednisone in an infant

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Autoimmune hemolytic anemia (AIHA) is characterized by shortened red cell survival due to the presence of autoantibodies directed against antigens on the red blood cell membrane. Corticosteroids and rarely intravenous immunoglobulin G are used in the treatment of AIHA.

We report a six-month-old boy with severe AIHA who initially responded to high dose methylprednisolone (HDMP) and intravenous immunoglobulin G (IVIG) therapies but eventually became refractory. He was then treated with low dose cyclosporine and prednisone successfully. In conclusion low dose cyclosporine and prednisone should be kept in mind in severe IHA.

Key words: autoimmune hemolytic anemia, cyclosporine, children.

Autoimmune hemolytic anemia (AIHA) is a disease characterized by the presence of autoantibodies directed against antigens on the red cell membrane. This phenomenon leads to premature red cell destruction by reticuloendothelial system phagocytes. In the severe form of the disease hemoglobin drops suddenly to life-threatening levels and, unfortunately, provision of compatible blood for transfusion is very difficult. In the treatment of AIHA, conventional dose prednisone (2 mg/kg/day), high dose methylprednisolone (3 mg/kg/day) or sometimes intravenous immunoglobulin G (IVIG) therapy are used. Other cytotoxic agents such as cyclosporine, azathioprine, and cyclophosphamide have rarely been reported to be used in refractory autoimmune hemolytic anemia.

Here, we report an infant with severe, refractory AIHA who was treated with alternate day cyclosporine and prednisone successfully.

Case Report
A six-month-old boy had been diagnosed to have Coombs’ positive hemolytic anemia at another hospital, and he received 13 units of red blood cell suspensions, prednisone (2 mg/kg/d) and IVIG therapy with a partial response. He was then admitted to our hospital with fever, pallor, mild icterus and splenomegaly (2 cm). His hemoglobin (Hb) was 5.8 g/dl with a reticulocyte count of 35%. His white blood cell (WBC) count was 23.9x10^9/L with 60% polymorphonuclear leukocytes (PNL), 36% lymphocytes and 4% band form and platelet count was 378x10^9/L. Direct antiglobulin test (DAT or direct Coombs’ test) was strongly positive consistent with the presence of warm, or IgG, autoantibodies. The antibody identification tests revealed panagglutination without any antigenic specificity. Antinuclear antibody (ANA) was negative and anti DNA was in normal limits. Serum IgG, IgM, IgA, and IgE levels were within normal age-matched range. Serologic tests for hepatitis viruses A, B, C, Epstein-Barr virus, cytomegalovirus (CMV), Parvovirus B-19 and human immunodeficiency virus revealed only positivity of CMV IgG. Blood, urine and throat cultures were negative. It was not possible to find compatible blood by in vitro tests. High dose methylprednisolone (HDMP) (30 mg/kg/d orally) and IVIG (0.5 g/kg/d for 5 days) were started. When Hb increased to 10 g/dl, the dose of methylprednisolone was tapered gradually and he was discharged home with prednisone, 2 mg/kg/d (Fig. 1).
Ten days later, he returned with a new hemolytic attack (Hb: 2.7 g/dl and reticulocyte count 40%) accompanied with generalized febrile convulsion and bronchopneumonia. Antibiotics and red cell suspension were given and methylprednisolone was restarted at 30 mg/kg/d orally (Fig. 1). Since his hemoglobin dropped suddenly when methylprednisolone dose was tapered under 15 mg/kg/d, it was maintained at that dose for a long period, then tapered very slowly. He became cushingoid and hypertensive requiring antihypertensive therapy (captopril).

While he was still receiving corticosteroids (methylprednisolone, 4 mg/kg/d), he developed a new hemolytic attack during an upper respiratory infection. His Hb dropped to 3.4 g/dl. It was impossible to find compatible red cells in in vitro tests. Biological compatibility was attempted carefully and the dose of methylprednisolone was increased to 30 mg/kg/d. With this dose of methylprednisolone and IVIG therapy his Hb initially increased but did not remain stable despite the ongoing HDMP. Cyclosporine was started at a dose of 4 mg/kg/d at two divided doses with prednisone (2 mg/kg/d), and hemolysis was controlled. The dose of cyclosporine and prednisone was then tapered to 2 mg/kg/day and 1 mg/kg/d, respectively. He was discharged with alternate day cyclosporine (2 mg/kg/d) and prednisone (1 mg/kg/d) (Fig. 1).

Within the following period, his hemoglobin was maintained within the normal range except for weak positive direct antiglobulin tests. No toxicity due to cyclosporine was seen. Nine months after starting cyclosporine, direct and indirect antiglobulin tests became negative and treatment was ceased. No further hemolysis was seen on his follow up of 12 months after cessation of the drugs and he continues to do well.

**Discussion**

Autoimmune hemolytic anemia in children may be associated with immunodeficiency syndrome, malignancy, and multisystem autoimmune disorders. Sometimes no underlying disease can be detected, as in our case. The pathogenesis of antierthrocyte autoantibody formation in AIHA is unclear but may involve an impaired immunoregulatory mechanism.\(^1^,^2\)

Immunosuppressive therapy with corticosteroids is the first line therapy of warm type AIHA and a response is seen in approximately 80% of cases. Corticosteroids are believed to inhibit Fc-receptor mediated clearance of IgG sensitized erythrocytes in the spleen, and may inhibit autoantibody synthesis.\(^1^,^2\) IVIG has a role in patients with AIHA who do not respond completely to conventional dose steroids. IVIG is able to produce a potent blockage of the reticulo-
endothelial system, thereby inhibiting phagocytosis of IgG sensitized red cells. Our patient did not respond completely to conventional dose steroids, and for this reason we initiated HDMP and IVIG therapy. He initially showed good response but at the time of his last hemolytic attack his Hb dropped again despite the HDMP. High dose methylprednisolone was less efficient than in his first attacks, which led us to use a more potent immunosuppressive drug.

The imbalance of T cell activation in favor of T4 cells may be responsible for autoantibody production. Cyclosporine is an immunosuppressive agent that interferes with T cell activation by inhibiting transcription of genes for interleukin-2 (IL-2), interferon-γ and several other cytokines. In this regard cyclosporine seems to be an ideal agent as its mechanism of action is to suppress helper T cell activity. Although cyclosporine is best known for its ability to inhibit rejection after solid organ transplantation and graft versus host disease after bone marrow transplantation, it has also proven to be effective in some refractory immune hematological diseases such as AIHA, immune thrombocytopenic purpura (ITP) Evans’ syndrome in adults and cyclosporine. In conclusion low dose cyclosporine with prednisone may be of benefit in patients with life-threatening AIHA.

REFERENCES

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