Case Report

Successful Use of Cyclosporine as An Adjunctive Immunosuppressive Agent in An Infantile Evans Syndrome: A Case Report and Literature Review

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Summary : *We report a successful treatment of cyclosporine in a 3-month-old female infant with Evans syndrome after a partial response to conventional IVIG and corticosteroids. With an implement of oral cyclosporine as an adjunctive treatment, most of hematological parameters have shown a notable improvement by 3-month maintenance therapy. No major complication was observed during treatment and this infant remained well at 6 months after cyclosporine cessation.*

In an infant with Evans syndrome who resisted to the first line medications, the second line immunosuppressive agent should be introduced in order to minimize autoantibody synthesis and to reduce the major side effects of long-term corticosteroids use. From the literature review, low dose cyclosporine appeared to be beneficial in refractory autoimmune cytopenia included Evans syndrome. However, limited number of infants were evaluated their responses after cyclosporine treatment in previously published reports.

Key Words : ● *Infant* ● *Evans syndrome* ● *Cyclosporine*

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Case report

A 3-month-old female infant presented with marked pallor, jaundice, hepatomegaly, and low grade fever for 3 days. Full blood count revealed hemoglobin level 3.7 g/dL, hematocrit 13.2%, MCV 120 fL, reticulocyte count 32.3%, WBC 12.3 x10^9/L, and platelets 422 x10^9/L. Numerous microspherocytes, polychromatic cells (as shown in Figure 1), hyperkalemia of 6.2 mmol/L serum potassium and strongly positive IgG direct anti-globulin test were identified for the diagnosis of autoimmune hemolytic anemia (AIHA). Otherwise related tests in this infant and her mother including serum immunoglobulin level, antinuclear antibody (ANA), anti-DNA, serologic markers for human immunodeficiency virus (HIV), hepatitis viruses A, B, C, Epstein-Barr virus (EBV), and Parvovirus B-19 were within normal range except for positive cytomegalovirus (CMV) IgG. Due to our concern of further hemolytic reaction in this condition, red blood cell transfusion was deferred. Intravenous methylprednisolone (5 mg/kg/day for 7 days) and IVIG (0.5 g/kg/day for 4 days) were started promptly as well as kayexalate enema to prevent cardiac arrhythmia from hyperkalemia. Hematocrit response after treatment was monitored and illustrated in Figure 2. Along with a reduction of hemolysis, methylprednisolone was tapered slowly at the beginning of the second week and the patient was discharged home at day 15 when

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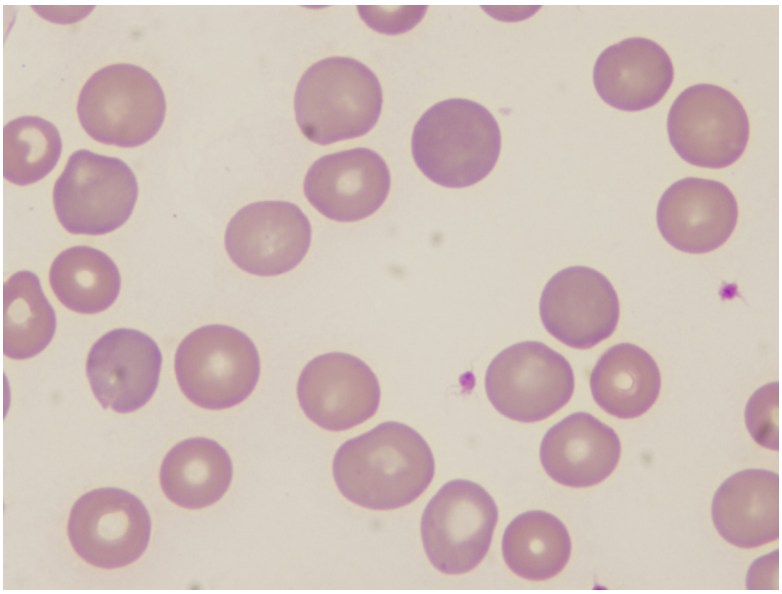

Figure 1. Numerous microspherocytes and polychromatic cells were identified in the peripheral blood smear of this infant

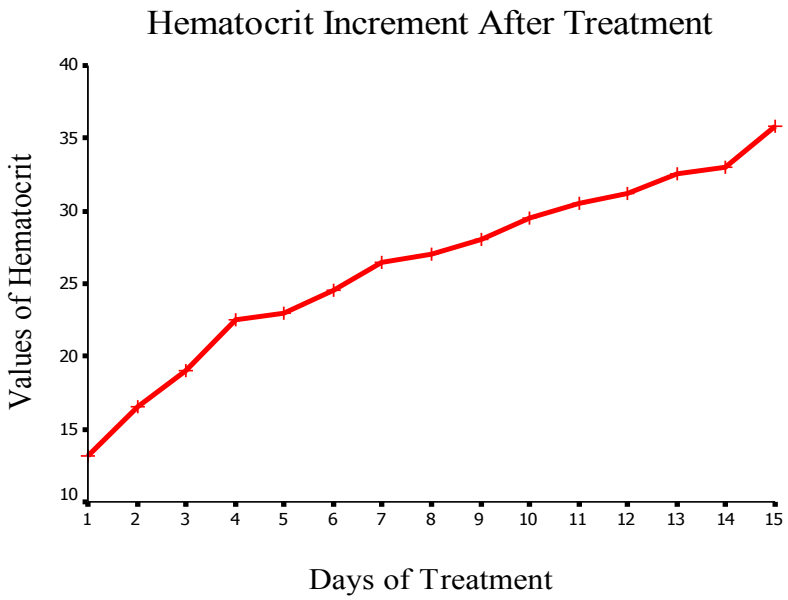

Figure 2 Hematocrit values (%) after the treatment of IVIG and methylprednisolone in the first AIHA episode

hemoglobin and hematocrit level of 11.4 g/dL and 35.8%, respectively without red blood cell transfusion. During this admission, hypertension was noted while the infant was on intravenous methylprednisolone.

Three weeks later, this infant was brought back to the hospital with generalized petechial rashes over the trunk and extremities after 2 days history of common cold. She was still on oral prednisolone at a dose of 0.5 mg/kg/day as a tapering part of her AIHA medication. Thrombocytopenia was detected with platelet count of $4.0x10^9$/L, hemoglobin 10.1 g/dL, hematocrit 30.4%, MCV 84.9 fL, reticulocyte count 13.9%, and WBC $10.7x10^9$/L with normal differential count. Direct Coombs test was also strongly positive which made her condition fulfilled the criteria of Evans syndrome. IVIG (1 g/kg/day for 2 days) was recommenced immediately after admission. Bone marrow aspiration was performed to exclude other possible causes of bicytopenia before oral prednisolone

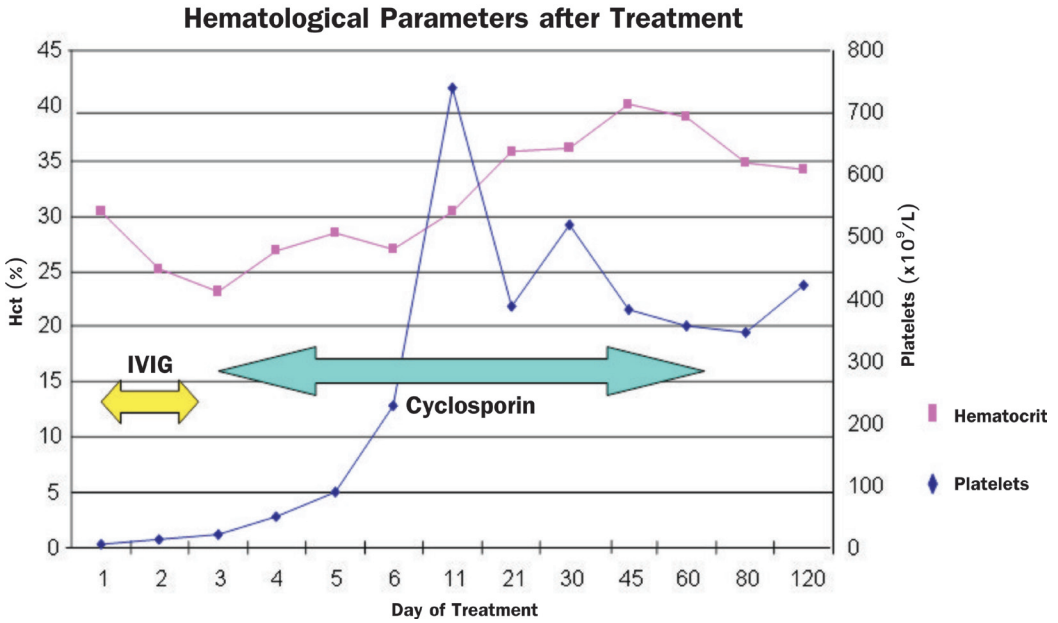

Figure 3 Hematological parameters after the treatment of Evans syndrome

dose was increased up to 2 mg/kg/day. On day 2 of admission, this patient developed severe vomiting and hyperglycemia, random blood glucose of 236 mg/dL with positive urine sugar. These manifestations were assumed to be acute complications of corticosteroids namely, steroid-induced gastritis and hyperglycemia. To lessen the adverse effects of corticosteroids in this infant, low dose cyclosporine (4 mg/kg/day in 2 divided doses) was constituted as an adjunctive immunosuppressive agent. Hematological values after treatment in the latter admission were described in figure 3 according to the day of treatment. On day 7 while hematocrit level and platelets were increasing, patient was discharged home with oral cyclosporine, reduced dose of oral prednisolone (1 mg/kg/day) and omeprazole.

Oral cyclosporine was gradually weaned off on day 90 and completely ceased on day 120 of follow-up when direct anti-globulin test became negative. During cyclosporine administration, only hirsutism was observed without other major adverse effects. At the most recent visit, which was 6 months after all medications termination, most hematological parameters maintained within their normal values.

Discussion

Evans syndrome was first described in 1951. The definition is ITP in company with AIHA with variable in time of onset and duration.[1] The median age at diagnosis of 7.7 years (range 0.2-26.6) was reported by North American Pediatric Survey.[2] Autoantibody against both red cell and platelet specific antigen, and T-cell dysregulation were responsible for the etiology in this entity.[3,4] For this reason, immunosuppressive and immunomodulating agents were administered to inhibit excess antibody synthesis. Despite of the treatment with IVIG and corticosteroids, recurrence of thrombocytopenia and anemia was still common and usually refractory. Cyclosporine was also considered as a second line immunosuppressor hampering T-cell activation and slowing down autoantibody formation.[5-10] No major toxic effects were associated with cyclosporine within the therapeutic dose range in 4-10 mg/kg/day for refractory immune cytopenia. Several reports have described clinical and laboratory improvement after a regimen which combined oral cyclosporine and prednisone for refractory Evans syndrome. However, the studies from an infant population were uncommon. Furthermore,

Table 1. Clinical data and treatment response from the literatures review of infantile Evans syndrome

Report	Patient Age (year)/ Sex	Initial Hematocrit (%)	Initial Platelet Count (x 10^9 /L)	Treatment	Response
McLeod AG, et al. [12]	0.3/ Female	17	48	Corticosteroids, IVIG, thymectomy, splenectomy	Good after splenectomy with 8 years follow-up time
Mathew P, et al. [2]	0.5/ NA	NA	NA	Corticosteroids, IVIG, splenectomy	Good after splenectomy within 1 week, follow-up time is NA
Scaradavou A, et al. [11]	0.5/ Male	27	7	Corticosteroids, IVIG, vincristine, danazol, cyclosporine	Therapy-dependent

NA; Not available

the effectiveness of cyclosporine use in Evans syndrome has been merely anecdotal and even controversial.

From our observation, cyclosporine was employed as a second line immunosuppressive agent, which minimizes the complications of an infant with Evans syndrome who received prior treatment with corticosteroids. Nonetheless, a latter episode of Evans syndrome has manifested while this patient was currently on oral prednisolone. Of these, the possibility of steroid resistance in this infant was expected. Rapid recovery of platelets without further hemolysis was examined shortly after an implementation of cyclosporine. After 3 months of oral cyclosporine treatment, abnormal hematological values were no longer observed, thus the maintenance treatment was able to stop accordingly. In addition, after the termination of cyclosporine for 6 months, this infant continued to be well-thriving with no recurrent hematologic disorders.

Up to present, infantile Evans syndrome were reported only in a limited number of cases as described in details of clinical data and treatment response in **table 1**. Hence no specific treatment guideline was widely established due to varieties of severity and response to individual therapeutic modality which were studied in previous publications.[11-14] Recently, rituximab or anti-CD20 monoclonal antibody was given in pediatric patients with Evans syndrome in order to deplete B-cells and reduce autoantibody production. Incidentally, several unfavorable effects and infections occurred in a significant number of patients who received rituximab treatment.[15, 16]

In conclusion, treatment of Evans syndrome in infants is still challenging. Acute and long-term consequences are the key barriers, as well as the high chance of recurrence. For relapse or refractory cases after the treatment of conventional IVIG and corticosteroids, cyclosporine as an adjunctive immunomodulator should be considered to enhance the chance of recovery.

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การใช้ยา Cyclosporine ในการรักษาผู้ป่วยทารกที่เป็นกลุ่มอาการ Evans ที่ไม่ตอบสนองต่อยากดภูมิคุ้มกันในขั้นต้น

สะการะ หัศภาดล, สุมิตรา วัฒนาธิษฐาน และ ปิติพร ศิริพัฒนพิพงษ์

ภาควิชากุมารเวชศาสตร์ คณะแพทยศาสตร์ มหาวิทยาลัยศรีนครินทรวิโรฒ

บทคัดย่อ : *รายงานผู้ป่วยเด็กทารกหญิงอายุ 3 เดือน มาพบแพทย์ด้วยอาการซีดอย่างรุนแรงภายในระยะเวลา 3 วัน ผู้ป่วยได้รับการวินิจฉัยด้วยภาวะ Autoimmune hemolytic anemia (AIHA) และมีผล Direct Coombs test เป็น 4+ หลังการรักษาด้วย IVIG และ Methylprednisolone ผู้ป่วยซีดน้อยลงและกลับบ้านได้โดยไม่ต้องได้รับเลือดเลย หลังจากนั้น 3 สัปดาห์ผู้ป่วยมีจ้ำเลือดออกตามผิวหนังและได้รับการวินิจฉัยว่าเป็นกลุ่มอาการ Evans จากการที่มีภาวะ AIHA ร่วมกับ Acute immune thromobocytopenic purpura (ITP) ทำให้ต้องได้รับยา IVIG และ Prednisolone ชนิดรับประทานในขนาดสูง และจากการใช้ยากลุ่ม Corticosteroids นี้ทำให้ผู้ป่วยมีปัญหากระเพาะอาหารอักเสบและน้ำตาลในเลือดสูง จึงต้องเพิ่มยากลุ่มที่กดภูมิคุ้มกันชนิดที่สองเข้าไปใช้แทนที่ Prednisolone ผลจากการได้รับยา Cyclosporine ชนิดรับประทานนาน 3 เดือน พบว่าผู้ป่วยหายขาดจากกลุ่มอาการ Evans หลังหยุดยาและติดตามการรักษานาน 6 เดือน นอกจากนี้ยังไม่พบผลข้างเคียงที่เป็นอันตรายกับทารกรายนี้*

Key Words : ● *Infant* ● *Evans syndrome* ● *Cyclosporine*

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