



Cyclosporin A therapy for steroid-dependent Henoch-Schönlein purpura

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Henoch-Schönlein purpura is one of the most common types of systemic vasculitis in children. Although recurrence is frequent, most cases are benign and self-limited. Standard treatment consists of supportive care and nonsteroid antiinflammatory drugs and/or steroid. Here we report 2 cases of Henoch-Schönlein purpura, both of which had a prolonged and corticosteroid-dependent disease course. After treatment with cyclosporin A, the symptoms and signs subsided gradually in both cases with no recurrence after tapering of corticosteroid and cyclosporin A.

Key words: Cyclosporin A, Henoch-Schönlein purpura

Henoch-Schönlein purpura (HSP) is the most common systemic vasculitis in children. The clinical manifestations include nonthrombocytopenic purpura, abdominal pain, arthralgia or arthritis and nephritis [1]. The clinical course of HSP is usually benign and requires only supportive treatment, but in some cases, severe gastrointestinal involvement, nephritis, and arthritis may occur with a high recurrence rate and more advanced treatment is necessary. Traditional treatment includes nonsteroidal antiinflammatory drugs with or without steroid. Other reported treatments include cyclophosphamide [2,3], plasmapheresis [4,5], azathioprine [6,7] and intravenous immunoglobulin [8, 9], these are associated with various effects. Here we report 2 patients who were refractory to supportive treatment and became steroid-dependent. After cyclosporin-A administration, the symptoms subsided gradually and steroid was discontinued. Although HSP is now considered to be an immune-complex disease [10], many reports have suggested that T lymphocyte regulation dysfunction may also play an important role in its pathogenesis [11,12]. Cyclosporin A (CsA) has been found to inhibit T-cell proliferation [13], which may be the reason why it was effective in these cases.

Case Report

Case 1

This 4-year-old boy had suffered from general weakness and multiple small palpable purpura over the buttocks

and bilateral lower extremities for 2 months. Henoch-Schönlein purpura was diagnosed and he was admitted to a local hospital. At the time of admission, the purpura had progressed to bilateral thighs, arms, and postauricular area. Tarry stool and severe abdominal pain with muscle guarding were noted. Laparotomy was performed but no bowel perforation was noted. After treatment with parenteral steroid, his symptoms improved gradually. Ten days later, while the steroid was being tapered, new purpura with abdominal pain and tarry stool were noted, and he was readmitted and received parenteral steroid treatment again. After his condition improved, he was discharged. However, bilateral leg purpura recurred which required re-admission for further evaluation and treatment.

After admission, parenteral solumedrol was given and purpura improved, but brownish color urine was noted the next day. Urinalysis showed hematuria (occult blood 4+; red blood cell 10-15/HPF) and proteinuria. Renal involvement was suspected and azathioprine was added. His condition improved and the steroid treatment was changed to oral prednisolone and gradually tapered at our outpatient clinic. However, skin purpura recurred and hematuria persisted. He was admitted twice to receive parenteral steroid (2 mg/kg/d) treatment during the next 2 months. Within the 4 months of treatment since the diagnosis of HSP, side effects of steroid treatment such as moon face, general edema, and obvious body weight gain (from 16 kg to 23 kg) developed. Because of persistent renal involvement (occult blood 3+, protein 30 mg/dL, red blood cell numerous/HPF) and recurrence of new skin purpura whenever steroid was tapered, CsA treatment was started with a dose of 100 mg/d (3-5 mg/kg/d). His skin rash disappeared gradually and urinalysis revealed no

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proteinuria and improved hematuria 2 weeks later. Prednisolone was tapered gradually and totally withdrawn 2 months later. Cyclosporin A was tapered and discontinued 1 week after prednisolone was withdrawn. The patient's condition was stable and he continues to receive regular outpatient department follow-up (Fig. 1A).

Case 2

This 5-year-old boy had suffered from general malaise, intermittent abdominal pain, and multiple skin purpura over all the extremities for 3 weeks. Swelling in all limbs and joints was noted with limited range of joint motion. Neither bloody stool nor gross hematuria was found. He was brought to a local hospital where HSP was diagnosed and intravenous steroid was prescribed. The skin rash and abdominal pain subsided gradually. However, the disease flared up with generalized skin purpura and abdominal pain when steroid treatment was discontinued. Therefore, the patient was transferred to our hospital for further evaluation and management. After admission, physical examination revealed drowsy consciousness, bilateral cheek swelling, multiple petechiae, and purpura over bilateral auricles and all extremities, and freely movable but edematous lower extremities. Intravenous solumedrol (equal to prednisolone 2 mg/kg/d) with azathioprine 2 mg/kg/d and Naposin 10 mg/kg/d were given under the diagnosis of HSP. Purpura and edema of the limbs improved gradually and steroid was changed to oral prednisolone 3 days later and then tapered gradually at the outpatient clinic. However, skin purpura recurred while prednisolone was being tapered. Although the dosage of prednisolone was then adjusted to 2 mg/kg/d, new skin purpura developed persistently. Due to the long-term use of steroid treatment, side effects including moon face and body weight gain (from 19 kg to 30 kg) progressively developed. Cyclosporin A was started with 100 mg/d (3-5 mg/kg/d). Skin purpura subsided gradually and oral prednisolone was tapered gradually and totally withdrawn 2 weeks later. Cyclosporin A was tapered to 50 mg/d 1 month later and discontinued after 2 months of use. The patient's condition was stable during regular follow up at the outpatient department for 1 year (Fig. 1B).

Discussion

Henoch-Schönlein purpura is the most common systemic vasculitis of children. The clinical presentations include nonthrombocytopenic palpable purpura over lower extremities and buttocks, arthritis or arthralgia, abdominal pain, and/or gastrointestinal

bleeding, hematuria, and proteinuria [1]. Some characteristics of this disease, such as elevated immunoglobulin (Ig) A level and IgA-mediated immune complexes deposition on skin biopsies, suggest an immune-mediated nature [10]. However, the pathogenic mechanism has not been demonstrated. Because the disease often occurs in winter and autumn [14] and children with HSP often have preceding upper airway infection, it has been suggested to be related to some kinds of infection [15].

Treatment for HSP is usually supportive and steroid is prescribed only in those patients with the complications of severe gastrointestinal or renal involvement [16]. However, long-term use of steroids is usually accompanied by side effects. In these 2 children, steroid treatment resulted in the development of severe body weight gain, moon face, and general edema. Since the disease flared up when the steroid dose was tapered and because of the development of severe side effects due to steroid treatment, use of other immunosuppressant drugs was considered. Treatment with cyclophosphamide [2,3], plasmapheresis [4,5], azathioprine [6,7], and intravenous immunoglobulin [8, 9] have all been reported in the treatment of steroid dependent HSP, but with controversial results. One case report described complete remission after CsA treatment in a patient with HSP and severe nephrotic syndrome [17]. In these 2 children, after CsA (3-5 mg/kg/d) treatment for 5 to 6 weeks, corticosteroid therapy was no longer needed and they were disease-free during 1 year follow up.

Cyclosporin A is a cyclic decapeptide derived from a soil fungus. The immunosuppressive mechanism of CsA occurs via interaction with T lymphocytes. Cyclosporin A can bind to cyclophilin (CyP), then the complex of CsA/CyP binds to calcineurin which prevents the production of interleukin (IL) -2. The

Table 1. Definition of symptom scores for Henoch-Schönlein purpura

Symptom	Score
Purpura	
Below umbilicus	1+
Above umbilicus	2+
Abdominal pain	
Stool OB <2+	1+
Stool OB >2+	2+
Arthralgia	1+
Renal involvement	
Urine OB 1+	1+
OB 2+	2+
OB ≥3+	3+

Abbreviation: OB = occult blood

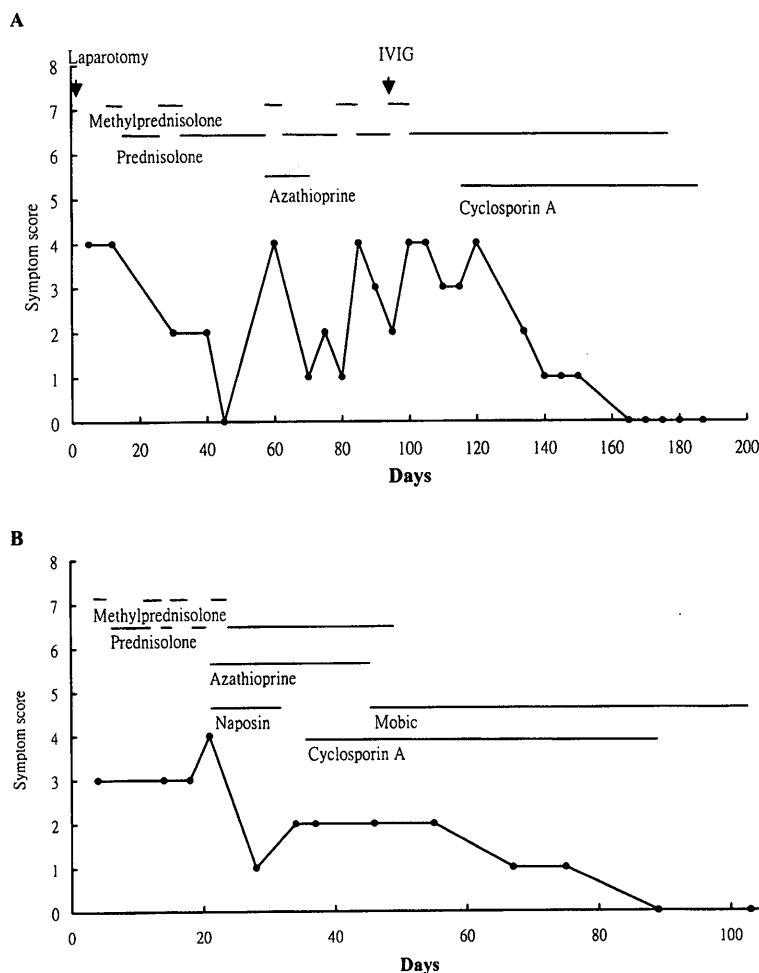


Fig. 1. Clinical course of Case 1 (A) and Case 2 (B). The symptom score is defined in Table 1.

cytokine IL-2 plays a critical role in the proliferation of T lymphocytes [13].

Autoantibodies such as IgA anticardiolipin antibodies have been found in patients with HSP and it has been hypothesized that these antibodies may interact with small vessels to form immune complexes deposition [18]. The production of these antibodies by B cells requires the help of CD4 T cells. Furthermore, some studies have suggested the significance of T lymphocytes in the pathogenesis of HSP. Sengar *et al* [11] reported a significant increase of CD4 helper T cells in HSP nephritis patients. In our previous study, peripheral T-cell growth factor- β secreting T cells (helper T cells type 3) were detected in children with acute HSP but not in normal controls or during the convalescent stage [12]. Cyclosporin A inhibits the proliferation and the function of T lymphocytes, which may explain why this drug can exert a therapeutic effect in HSP patients.

In conclusion, although childhood HSP is often benign, in some cases with severe complications or steroid dependency, CsA may provide an effective treatment alternative.

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