Efficacy of cyclosporine a for steroid-resistant severe henoch-schönlein purpura nephritis

Fukushima J. Med. Sci.,
Vol. 59, No. 2, 2013

[Case Report]

EFFICACY OF CYCLOSPORINE A FOR STEROID-RESISTANT SEVERE HENOCH-SCHÖNLEIN PURPURA NEPHRITIS

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(Received March 8, 2013, accepted September 13, 2013)

Abstract : Aggressive treatment is necessary for continuous high-range proteinuria in cases of pediatric Henoch-Schönlein purpura nephritis (HSPN) as the long-term prognosis is sometimes poor. Cyclosporine (CyA) has immunosuppressive effects as well as a very selective inhibitory effect on T-helper cell function. Here we report two 7-year-old boys with steroid-resistant HSPN treated with CyA. After diagnosis of HSPN, we treated both patients with methylprednisolone and urokinase pulse therapy (MUT) combined with multiple drugs ; however, high-range proteinuria persisted and CyA was added to the treatment regimen. The proteinuria subsequently decreased gradually and pathological findings at the second renal biopsy were improved. Furthermore, neither patient showed any adverse effects, such as hypertension, encephalopathy, or chronic nephrotoxicity, to the CyA treatment.

In conclusion, these results suggest that CyA may be a safe and effective treatment for steroid-resistant severe HSPN.

Key words : Henoch-Sch. ANvnlein purpura nephritis, cyclosporine A, proteinuria

INTRODUCTION

Henoch-Schönlein purpura (HSP) is one of the most common forms of vasculitis manifested in childhood. HSP is an immunoglobulin (Ig) A-mediated immune-complex vasculitis that predominantly affects the skin, joints, gastrointestinal tract and kidneys[1-4]. Renal involvement is observed in between 20 and 80% of cases. The majority of children with Henoch-Schönlein purpura nephritis (HSPN) have a good chance of recovery ; however, renal involvement is occasionally severe[2, 3]. High-range proteinuria, glomerular crescentic nephritis and rapidly progressive glomerular nephritis are poor prognostic factors for HSPN[1, 4]. In cases of continuous high-range proteinuria associated with HSPN, aggressive treatment is necessary as the prognosis is sometimes poor.

With regard to the treatment of severe HSPN, the results obtained so far are controversial ; however, most published reports emphasize immunosuppressive therapy[5-11]. Some studies have dealt with the use of multiple combined agents, including cyclophosphamide (CPM), and/or methylprednisolone and urokinase pulse therapy (MUT)[5-7]. However, CPM can result in some severe adverse effects, such as gonadal dysfunction and secondary cancer[8]. Therefore, the use of safer immunosuppressive agents is recommended. Mizoribine (MZB) is partially effective for severe HSPN in place of CPM as part of a combination therapy, and is characterized as a safe and well-tolerated drug. However, MZB is not so effective for HSPN in patients demonstrating continued high levels of urinary protein exertion or histologically severe HSPN with >50% crescents[21]. Recently, there have been a few reports on the use of cyclosporine A (CyA) as an initial treatment for severe HSPN involving high-range proteinuria[9-11, 23]. Here we report the efficacy of CyA in the treatment of two 7-year-old boys

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with steroid-resistant severe HSPN.

CASE 1

A 7-year-old boy developed a purpuric rash on the lower extremities. On the following day, he presented with abdominal pain, nausea and bloody stool, and his purpura had worsened. He was referred and admitted to a local hospital with a diagnosis of HSP. Physical examination revealed slight edema, and urinalysis showed proteinuria and hematuria on admission. Prednisolone (1 mg/kg) treatment was initiated to reduce the purpura, abdominal pain and bloody stool ; however, no improvements in abdominal pain, purpura, or proteinuria (3～4 g/day) were observed. The patient was then referred to our hospital.

On admission, slight edema of the eyelids and pretibial region, and a purpuric rash on the pretibial region were noted. The patient was 120.8 cm in height, with a body weight of 19.8 kg and blood pressure of 112/76 mmHg. No other abnormalities in his vital signs were observed. Laboratory examination (Table 1) revealed hypoproteinemia (total protein 5.4 g/dl, serum albumin 2.7 g/dl), hyperlipidemia (triglyceride 258 mg/dl, total cholesterol 242 mg/dl) and hypogammaglobulinemia (IgG 364 mg/dl, IgM 150 mg/dl and IgA 289 mg/dl). Renal function had not deteriorated (serum creatinine 0.30 mg/dl, 24 h creatinine clearance (24-hCcr) 152.7 ml/min per 1.73 m^2 body surface area). Immunological studies revealed a third component of complement level (C3, normal range 69-128 mg/dl) of 152 mg/dl, C4 (14-36 mg/dl) of 30 mg/dl, CH50 (30-45 U/ml) of 45 IU/ml, an anti-nuclear antibody titer of 160 and anti-dsDNA antibodies <5.0 IU/ml. Additional findings were as follow : factor XIII activity ; 53.1%, titer of hepatitis B virus antibodies ; negative, titer of hepatitis C virus antibodies ; negative and titer of syphilis antibodies ; negative. Urinalysis revealed protein excretion of 4.0 g/day ; β-2MG 0.2 μg/ml ; NAG 14.5 U/l ; and sediment containing many erythrocytes and 50 to 99 leukocytes per high-power field, and 10 to 19 granular casts per low-power field.

A first renal biopsy was performed on his 4th day of hospitalization (Fig. 1). Immunofluoresence microscopy showed, C3, Fibrinogen, IgM and IgA deposits with a granular pattern. Light microscopy (LM) revealed severe mesangial proliferation with cellular crescents. These findings were observed in approximately 25% of the glomeruli obtained.

Table 1. Results of laboratory findings on admission for Case 1

RBC	485 ×10^4/mm^3	TP	5.4 g/dl	Urinalysis	
Hb	13.3 g/dl	ALB	2.7 g/dl		
Hct	39.20%	Alb	56.20%	Urine Protein	4.0 g/day
PLT	24.2×10^4/mm^3	α1-gl	4.60%	Sediment	
WBC	7,600/mm^3	α2-gl	14.90%	RBC	100< /HPF
		β-gl	14.40%		
IgG	364 mg/dl	γ-gl	9.90%	WBC	50-99/HPF
IgA	289 mg/dl	AST	16 U/L	Cast	10-19/LPF
IgM	150 mg/dl	ALT	5 U/L		
C3	152 mg/dl	LDH	164 U/L	u-β2MG	0.2 μg/ml
C4	30 mg/dl	ALP	312 mg/dl	u-NAG	14.5 U/l
CH50	45 IU/ml	BUN	5.1 mg/dl		
Anti-nuclear	< ×160	Cr	0.30 mEq/L	24HCCR	152.7 ml/min/1.73 m^2
antibody		Na	139 mEq/L		
Anti-dsDNA	<5.0 IU/ml	K	3.6 mEq/L		
antibody		Cl	101 mg/dl		
PT INR	0.93	Ca	9.0 mg/dl		
APTT	28.9 sec	P	5.4 mg/dl		
Fib	467 mg/dl	TC	205 mg/dl		
		TG	258 mg/dl		
Factor 13	53.10%	HDL-C	47 mg/dl		
ASO	28 IU/ml	CRP	1.52 mg/dl		
β2MG	1.75 μg/ml				

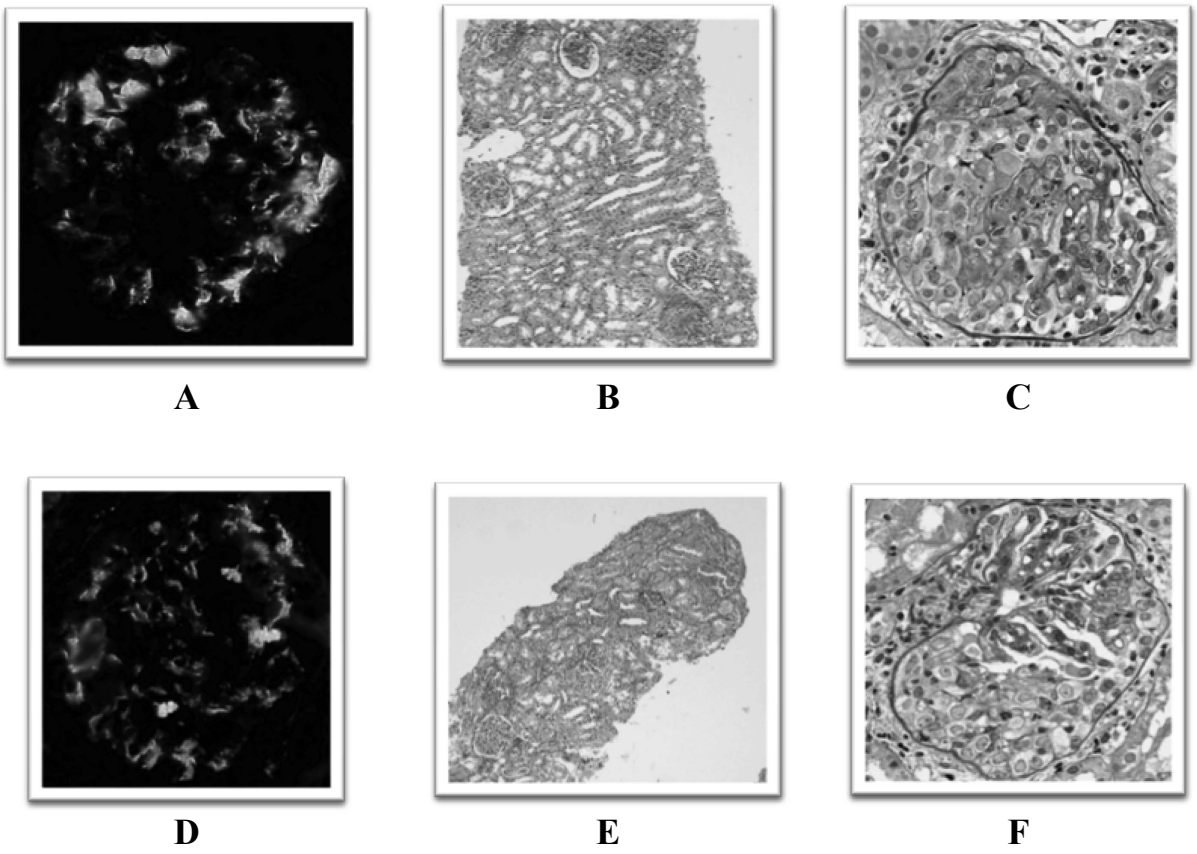

Fig. 1. Pathological findings from the renal biopsies.
A : IF microscopic examination at the first renal biopsy for Case 1 showed IgA deposits in the mesangial region. (×400)
B : LM revealed severe mesangial proliferation with cellular crescents. PAS stain (×100)
Twelve of 53 glomeruli (22.6%) showed cellular crescent formation.
C : LM revealed a cellular crescent. PAS stain (×400)
D : IF microscopic examination at the first renal biopsy for Case 2 showed IgA deposits in the mesangial region. (×400)
E : LM revealed severe mesangial proliferation with cellular crescents. PAS stain (×100)
Ten of 29 glomeruli (34.5%) showed cellular crescent formation.
F : LM revealed cellular crescents. PAS stain (×400)

Histological severity was scored as grade IIIb according to International Study of Kidney Disease in Children (ISKDC) classification. He was diagnosed with HSPN and nephrotic syndrome.

We performed MUT combined with multiple drugs (Fig. 2). MUT consisted of a combination of pulse methylprednisolone at 30 mg/kg/day i.v. bolus for three consecutive days, and pulsed urokinase (UK) at 5,000 units/kg/day i.v. bolus, followed by daily oral prednisolone, (1 mg/kg/day), along with anti-platelet agents (dipyridamole 5 mg/kg/day), an anti-coagulant (warfarin 0.5 mg/day), and a HMG-CoA reductase inhibitor (simvastatin 10 mg/day). However, high-range proteinuria (2～3 g/day) persisted after the start of this treatment. Therefore, we added angiotensin convert enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB) and mizoribine (MZB : 150 mg/day) to the treatment regimen. MZB was given orally once a day. As the high-range proteinuria had not decreased by two months after the start of MZB treatment, we started CyA administration in place of MZB. The proteinuria decreased gradually after the change from MZB to CyA, and CyA was given orally twice per day for 13 months to maintain the plasma trough level between 50 and 100 ng/ml. Prednisolone administration was thereafter tapered gradually and completely withdrawn 8 months after discharge. CyA was discontinued after treatment for 13 months, and no proteinuria was detected despite the presence of microscopic hematuria. A second renal biopsy was performed at 15 months after the onset of symptoms. LM revealed slight mesangial proliferation and an increase in the mesangial matrices, but no

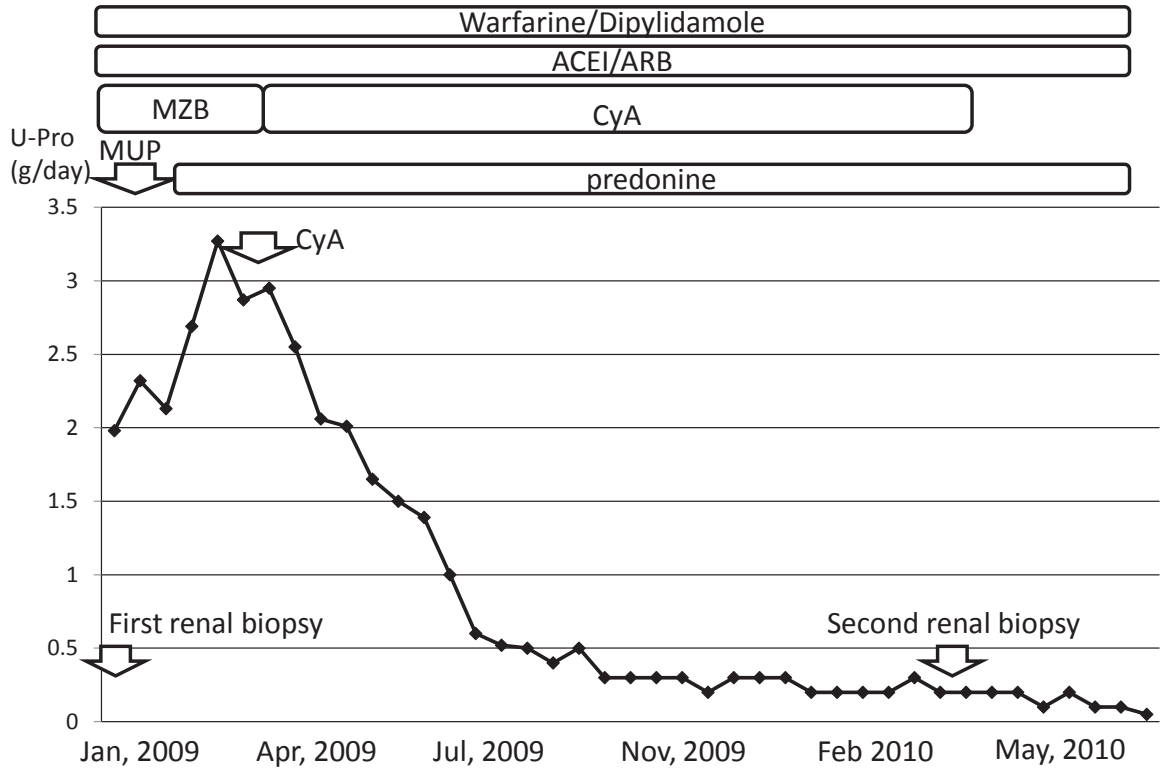

Fig. 2. Clinical course for Case 1.

CyA nephrotoxicity was observed.

CASE 2

A 7-year-old boy was referred and admitted to our hospital with high-range proteinuria due to HSPN. On admission, slight edema of the eyelids and a purpuric rash on the pretibial region were noted. Laboratory examination revealed hypoproteinemia (total protein 5.0 g/dl, serum albumin 3.1 g/dl), hyperlipidemia (total cholesterol 328 mg/dl), hypogammaglobulinemia (IgG 215 mg/dl) and high-range proteinuria (4.6 g/day). Renal function was normal. A first renal needle biopsy was performed (Fig. 1), and the patient was scored as grade IIIb according to the ISKDC classification. He was diagnosed with HSPN and nephrotic syndrome.

We performed MUT combined with multiple drugs. After MUT, prednisolone (1 mg/kg/day) along with anti-platelet agents (dipyridamole 5 mg/kg/day), an anti-coagulant (warfarin 0.5 mg per day), an HMG-CoA reductase inhibitor (simvastatin 10 mg/day), and ACEI and ARB were given. Nevertheless, high-range proteinuria (4 g/day) persisted after the start of this treatment. Therefore, we added MZB to the treatment regimen. However, as the proteinuria had not decreased by two months after the start of MZB administration, we started CyA administration in place of MZB. Subsequently, the level of proteinuria was reduced. CyA was given orally twice per day dose for 14 months to maintain the plasma trough level between 60 and 100 ng/ml. Prednisolone administration was thereafter tapered gradually and completely withdrawn 12 months after discharge. CyA was discontinued after 14 months, and no proteinuria was detected despite the presence of microscopic hematuria. A second renal needle biopsy was performed at 18 months after the onset of symptoms. As in Case 1, LM revealed slight mesangial proliferation and an increase in mesangial matrices, but no CyA nephrotoxicity.

DISCUSSION

High-range proteinuria has been reported to be a risk factor for the development of chronic renal insufficiency in HSPN[4]. Beyond this, the prognosis cannot be predicted by the results of the first renal biopsy, and the decision to start immunosuppressive treatment in HSPN should be based on the clinical presentation rather than on biopsy findings alone[12]. As for the treatment of severe HSPN, some studies have dealt with the use of combination therapies including intravenous pulses of steroids, immunosuppressive agents, dipyridamole, warfarin,

ARB/ACEI and plasmapheresis, as described previously[13]. We have reported the efficacy methylprednisolone and urokinase pulse therapy combined with cyclophosphamide (CPM) for children with severe HSPN involving high-range proteinuria[5].

CPM is a potent alkylating agent that inhibits lymphocyte proliferation, leading to the repression of B and T lymphocyte function as well as to a reduction in their numbers. To date, CPM has been used with success in the treatment of HSPN and several other forms of minimal-change nephritic syndrome and crescentic glomerulonephritis, particularly those characterized by altered auto-immunity, including Wegener's granulomatosis and systemic lupus erythematosus[5, 7, 14]. On the other hand, CPM can result in some severe adverse effects, such as myelosuppression, hemorrhagic cystitis, gonadal dysfunction and secondary cancer[8, 15]. Therefore, a safer immunosuppressive agents is recommended for use.

MZB is an antimetabolite that exerts an immunosuppressant effect by inhibiting lymphocyte proliferation. It is effective for nephritic syndrome, lupus nephritis, and IgA nephropathy, and is characterized as a safe and well-tolerated drug. We reported the administration of MZB in place of cyclophosphamide as part of a combination therapy for severe pediatric HSPN. However, MZB is not as effective for HSPN patients demonstrating continuous high levels of urinary protein exertion or histologically severe HSPN with >50% crescents.

On the other hand, CyA is a cyclic lipophilic undecapeptide that has immunosuppressive effects as well as a very selective inhibitory effect on T-helper cell function. Initially used in transplantations to control tissue rejection, CyA has more recently been used for the treatment of a wide range of autoimmune diseases. There have been a few reports of combined therapy with multiple drugs, including CyA for severe HSPN involving high-range proteinuria[9-11]. Someya *et al*. first reported the success of treatment with CyA for HSPN (ISKDC IIIb) involving high-range proteinuria that was resistant to methylprednisolone pulse therapy in Japan[9]. Shin *et al*. have also reported the efficacy of CyA in inducing a remission in a subset of HSPN (ISKDC II-IVb) patients with nephrotic syndrome, and they noted that the histological activity index was significantly decreased at the second biopsy. Recently, Jee *et al*. analyzed the clinical outcomes of 29 HSPN patients with nephritic-range proteinuria treated with CyA. They concluded that CyA treatment for HSPN showing nephritic-range proteinuria is safe and very effective[23]. They also suggested that early aggressive immunosuppression may ameliorate histological progression. Both patients reported here were treated with MUT combined with multiple drugs immediately after diagnosis of HSPN ; however, high-range proteinuria persisted and CyA was added to their treatment regimen. Subsequently, the proteinuria decreased gradually and pathological findings at the second renal biopsy were improved.

The clinical efficacy of CyA for HSPN has not been well documented. The mechanism underlying the effects of CyA for HSPN are speculated as follows ; 1) CyA has long been considered to interfere with the production of interleukin-2 and other lymphokines from T lymphocytes[11] and 2) its antiproteinuric effect can be explained by its direct effects on the actin skeleton of podocytes, not by its actions on T lymphocytes[17, 18].

Treatment with CyA can lead to some adverse effects, including hypertension, encephalopathy, and chronic nephrotoxicity ; however, it has few severe adverse effects, such as hemorrhagic cystitis, gonadal dysfunction or secondary cancer[19, 20]. With regard to CyA nephrotoxicity (CyAN), in particular, it is known to be primarily caused by chronic ischemic insult to kidney, resulting in arteriolar hyalination and tubulointestitial changes, including striped intestinal fibrosis, tubular vacuolization, and atrophy[20]. It is well known that the administration of high-dose CyA (plasma trough level >100 ng/ml) over 2 years is a risk factor for CyAN[22]. In our cases, no acute-phase adverse effects, such as hypertension or CyA encephalopathy, were observed. Further, histological findings were improved in the two patients at their follow-up biopsy and no characteristic lesions associated with chronic CyAN were noted. As the plasma trough level of CyA was kept at between 50 and 100 ng/ml for about twelve months, it is thought that the risk of CyA chronic nephrotoxicity was low, while the administration of this low dose of CyA was effective for our HSPN patients. These results suggest that the administration of CyA is both effective and safe for steroid-resistant severe HSPN patients.

In conclusion, these results suggest that CyA may be safe and effective in the treatment of steroid-resistant severe HSPN.

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