An adult case of severe steroid-resistant Henoch–Schönlein purpura nephritis treated with intravenous cyclophosphamide and tonsillectomy

Emi Sasaki^{1,2} · Maki Shibata¹ · Asami Kato¹ · Naoto Hamano¹ · Takashi Katsuki¹ · Manami Tada¹ · Fumihiko Hinoshita¹

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Abstract A previously healthy 37-year-old Canadian man living in Japan visited a hospital in Thailand while traveling because of edematous legs, purpura, arthralgia, bloody stool, and fever after an insect bite. Henoch–Schönlein purpura (HSP) was suspected. His creatinine level was 5.2 mg/dL. He was treated with oral prednisolone (PSL) and oral cyclophosphamide (CPA); after treatment, his creatinine level improved to 2.4 mg/dL. Upon returning to Japan, he was admitted to the National Center for Global Health and Medicine Hospital in Tokyo. A kidney biopsy was performed, and HSP nephritis (HSPN) was diagnosed. Renal dysfunction and proteinuria persisted despite 4 administrations of steroid-pulse therapy and 3 sessions of plasma exchange. Finally, he was treated with intravenous cyclophosphamide (IVCY). His creatinine level and proteinuria markedly improved. His microscopic hematuria disappeared after he underwent tonsillectomy. There have been only a few case reports describing patients with adult-onset HSPN necessitating IVCY. We present here a rare case of steroid-resistant HSPN treated with IVCY and tonsillectomy, with reference to some recent findings.

Keywords Henoch–Schönlein purpura (HSP) · Nephrotic syndrome · Intravenous cyclophosphamide therapy

(IVCY) · Cyclophosphamide (CPA) · Prednisolone (PSL) · Tonsillectomy

Introduction

Henoch–Schönlein purpura (HSP) is a systemic vasculitis with a prominent cutaneous component, and is characterized by tissue deposition of IgA-containing immune complexes.

The classic tetrad of HSP is rash, arthralgia, abdominal pain, and renal disease, which can develop in any order and at any time over a period of several days to several weeks [1]. HSP occurs more often in children than adults, but renal involvement is more likely to occur and to be more severe in older children and in adults, prompting more aggressive therapy [2].

In general, HSP is treated with corticosteroids. However, corticosteroid therapy is not very effective in some severe cases that include HSP nephritis (HSPN). Treatment for severe HSPN in adults has not been established and is still controversial. There have been few previous case reports on HSPN treated with intravenous cyclophosphamide (IVCY). There has been only one case report in the Japanese literature and a report of 3 cases in the English literature, which did not provide the important clinical findings in detail. Here, we present a rare and instructive case of severe HSPN successfully treated with IVCY.

Case report

A 37-year-old Canadian man traveling in Thailand during the summer of 2012 was bitten by an unknown insect. After that, his legs became edematous, and purpura, arthralgia,

✉ Emi Sasaki
esaskid@tmd.ac.jp

¹ Department of Nephrology, National Center for Global Health and Medicine Hospital, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan

² Present Address: Tokyo Medical Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-0034, Japan

and fever appeared (Fig. 1). Although he visited several hospitals in Thailand, the cause of his illness could not be determined. Two weeks later, he had abdominal pain and bloody stool, and went to another hospital in Thailand, where he underwent esophagogastroduodenoscopy (EGD). A gastric ulcer was found, and HSP was suspected. At that time, his creatinine level rose to 5.2 mg/dL, and he was hospitalized on the spot. He was treated with intravenous dexamethasone, followed by oral prednisolone (PSL) 80 mg and oral cyclophosphamide (CPA) 100 mg. After this treatment, his creatinine level decreased to 2.4 mg/dL and his abdominal pain temporarily improved. Fourteen days after admission, he returned to Japan.

Fig. 1 Lower legs show a diffuse purpuric rash. Photographed in Thailand

After returning to Japan, his abdominal pain became severe again, and he called the ambulance. On admission at our hospital, he was febrile (body temperature 37.1 °C), his blood pressure was 138/76 mmHg, pulse rate was 79 beats per min, and oxygen saturation was 97 % (room air). Physical examination showed his palpebral conjunctiva to be anemic. His bowel sounds were decreased, and spontaneous pain and tenderness were found in the lower abdomen.

There was no abnormality in the heart or chest. Systemic edema was apparent, and the patient's body weight markedly increased from 85 to 114 kg. There was diffuse purpura with pigmentation on both legs. Laboratory data on admission are shown in Table 1. The outstanding findings are summarized as follows: anemia [hemoglobin (Hb) 6.8 g/dL], hypoalbuminemia (serum Alb 1.2 g/dL), renal failure with elevated serum blood urea nitrogen (BUN) 74.9 mg/dL and creatinine (Cr) 2.43 mg/dL, decreased immunoglobulin G (IgG) level (serum IgG 243 mg/dL), proteinuria (urine protein excretion 13.7 g/day), and gross hematuria [urine red blood cells (RBC) >100 high power field]. Although EGD was performed again, there was no evidence of upper gastrointestinal tract bleeding. Considering that the clinical symptoms involved organ and laboratory findings in this case, the Birmingham Vasculitis Activity Score (BVAS) [22] was 27/63 points. Kidney biopsy was performed on the 7th hospital day to determine the cause of the patient's nephrotic syndrome. Light

Table 1 Laboratory data on admission to NCGM hospital

Urinalysis		Blood chemistry		Immunological tests	
Protein	3+	TP	3.3 g/dl	IgG	243 mg/dl
	13.7 g/day	Alb	1.2 g/dl	IgA	108 mg/dl
Occult blood	3+	AST	23 IU/l	IgM	86 mg/dl
Sediment		ALT	22 IU/l	ANA	–
RBC	>100/HPF	LDH	202 IU/l	MPO-ANCA	–
Granular casts	1+	ALP	140 IU/l	PR3-ANCA	–
		yGTP	36 IU/l	Cryoglobulin	–
Blood Count		Amy	151 IU/l	C3	81 mg/dl
RBC	$230 \times 10^4/\mu\text{l}$	CK	236 IU/l	C4	25.4 mg/dl
Hb	6.8 g/dl	BUN	80.3 mg/dl	ASO	76 IU/ml
Ht	20.1 %	Cr	2.59 mg/dl	ASK	<160 IU/ml
WBC	15,310/ μl	Na	139 mEq/l	Selectivity index	0.24
Neutrophil	94 %	K	4.6 mEq/l		
Eosinophil	0 %	Cl	107 mEq/l		
Lymphocyte	5 %	Ca	7.3 mg/dl		
Plts	$285 \times 10^3/\mu\text{l}$	p	6.1 mg/dl		
		T-cho	189 mg/dl		
Inflammation		LDL-cho	104 mg/dl		
ESR	35 mm/h	HDL-cho	25 mg/dl		
CRP	0.72 mg/dl				

ANA antinuclear antibody, MPO-ANCA myeloperoxidase-anti-neutrophil cytoplasmic antibody, PR3-ANCA proteinase-3 anti-neutrophil cytoplasmic antibody

Fig. 2 Light microscopy findings. **a** Cellular crescents, **b** segmental sclerosis, **c** endocapillary proliferation, **d** advanced hyperplasia of the mesangial cells and lobulation, **e** inflammatory cell infiltration to

microscopy revealed cellular crescents in 15 glomeruli out of 27 (56 %) (Fig. 2a), segmental sclerosis in 1 glomerulus out of 27 (4 %) (Fig. 2b), and normal or mesangial proliferation in 11 glomeruli out of 27 (40 %). Also observed were endocapillary cell proliferation (Fig. 2c), advanced hyperplasia of the mesangial cells, and lobulation in some of the glomeruli (Fig. 2d). Mononuclear leukocytes, such as lymphocytes, monocytes, and plasma cells, were the main constituents in the interstitial infiltration area (Fig. 2e); neutrophils and eosinophils did not infiltrate this

some renal tubules, and **f** tubulointerstitial lesion. **a–d**, **f** $\times 400$, periodic acid-Schiff (PAS) stain, **e** $\times 200$, hematoxylin and eosin (HE) stain

area. Some renal tubules had inflammatory cell infiltration (Fig. 2f). A mainly granular, partially capillary, and mesangial staining pattern of IgA and C3 could be observed (Fig. 3a, b). The patient was diagnosed as having HSPN. For a summarized pathological diagnosis, we used the pathological score of the International Study of Kidney Disease in Children (ISKDC). According to this classification, the glomerular changes were shown to be grade IV.

Treatment with steroid-pulse therapy (methylprednisolone 1000 mg/day for 3 days) was started and repeated

Fig. 3 Immunofluorescence findings of the patient's renal pathology: IgA(+), IgG(–), IgM(–), C1q(–), C3(+), C4(–), and fibrinogen(–). **a–b** $\times 400$, IF

every week for 2 weeks. Antiplatelet therapy using clopidogrel sulfate (75 mg/day) was also started. However, there was no improvement in the proteinuria, hematuria, or renal dysfunction, even after the patient received steroid-pulse therapy twice. Plasma exchange (PE) (4500 mL/day for 3 days) was performed. Even after the PE, no improvement was found. Additional steroid-pulse therapy at the same dose as at the beginning was repeated 2 more times within 2 weeks, but the HSPN was apparently steroid resistant. Since no further improvement was achieved with these treatments, intravenous cyclophosphamide (IVCY, 1000 mg/day) was administered after the 4th steroid-pulse therapy and PE. IVCY was repeated every 2 weeks. No marked side effects were found.

With repeated IVCY, the patient's proteinuria and renal dysfunction gradually improved. After finishing the 4th round of IVCY, his serum creatinine level and proteinuria decreased to 1.6 mg/dL and 3.6 g/day, respectively, and the dose of oral prednisolone was gradually tapered (Fig. 4). Then, azathioprine was started as maintenance therapy. Consequently, it was confirmed that the IVCY was

very effective for his nephrotic syndrome and renal dysfunction.

The patient was discharged on the 107th hospital day. Seven weeks later, he was admitted again for a 5th round of IVCY. At that time, his creatinine level was 1.8 mg/dL and the amount of proteinuria decreased to 0.8 g/day. Eight months after the 1st admission, his proteinuria disappeared. The total amount of cyclophosphamide (oral and intravenous) used was about 8 g under our treatment. The patient had wanted to undergo tonsillectomy before he became ill with HSPN, because he reported that he had frequently experienced high fever with tonsillitis. On the 217th day, he underwent tonsillectomy of his own will. After that, his hematuria apparently decreased and finally disappeared at 10 months after tonsillectomy. Although his recent Cr level measured 1.6 mg/dL, he persistently has had no proteinuria and no hematuria. His HSPN remains in remission.

Discussion

Approximately half of the cases with HSP are preceded by an upper respiratory infection, especially streptococcal infection. Other infectious agents, vaccinations, and insect bites also have been implicated as possible triggers for HSP. Henoch–Schönlein purpura occurs mainly in fall, winter, and spring, and rarely in summer [3–5]. The present patient had no episode of infection or vaccination; he became sick after an insect bite. The insect bite might have been a trigger of HSP in his case.

Although there were a few areas of glomerular sclerosis, and crescents were almost all cellular, his Cr level did not improve to a normal level, even though his proteinuria and hematuria disappeared. Therefore, it might be suggested that his HSPN had been rather severe and that no persistent therapy for HSPN at the beginning in Thailand might possibly have produced a therapeutic response.

Most studies have found that renal involvement in HSP tends to be more severe in adults than in children, as manifested by a higher incidence of nephrotic syndrome, hypertension, and elevated Cr levels [1]. However, there are no definitive treatments, partly because only a small number of adults experience severe HSPN. The present patient was initially treated by a corticosteroid after kidney biopsy. It has been stated that oral glucocorticoids produce a genomic effect through their receptors; a steroid pulse produces a non-genomic effect, which induces apoptosis of the lymphocytes by acting on cell membranes directly [23]. Unfortunately, the patient's HSPN was steroid resistant. There have been case reports on the efficacy of cyclosporine [7], intravenous immunoglobulin [8], PE [9, 10], and tonsillectomy [11, 12] in patients resistant to

Fig. 4 Patient's clinical course. *IVCY* intravenous cyclophosphamide, *AZA* azathioprine, *CPA* oral cyclophosphamide, *PSL* prednisolone, *PE* plasma exchange, *s-Cr* serum creatinine, *u-protein* urinary protein

traditional immunosuppressants. Although tonsillectomy is recommended for IgA nephropathy, at least in Japan [13, 14], there has been no clinical evidence that tonsillectomy is also effective for HSPN, as far as we know. Tonsillectomy is performed to remove focal infection that causes inflammation. In the present case, the patient's hematuria remained, although his proteinuria had already disappeared. We expected that tonsillectomy would reduce the patient's hematuria and prevent recurrence of HSPN by reducing IgA production and minimizing the patient's abnormal immune response and inflammatory events following glomerular IgA deposition.

Plasma exchange has also been used in a number of patients with severe HSPN, usually with crescentic glomerulonephritis and rapidly progressive renal failure.

The efficacy of PE is still controversial, and there are potential side effects. However, a few previous reports have suggested that PE alone may be curative in some patients with HSPN if instituted early in the course of the disease [9, 10]. PE removes IgA-containing immune complexes, aggregates or proinflammatory mediators (cytokines and components of the complement system), and also reduces fibrinogen and other coagulation factors. We conjectured that PE would still be effective for this patient and performed it, because his renal pathological findings contained few areas of interstitial fibrosis or glomerular sclerosis. However, PE was not effective for this patient. It seems that the timing for performing PE was too late for treating his severe HSPN. If PE had been performed when his rapidly progressive glomerulonephritis (RPGN) was

active in Thailand, it might have been effective. Cyclophosphamide is a potent alkylating agent that inhibits lymphocyte proliferation, which leads to the repression of B and T lymphocyte functions as well as reducing their number. Although the patient had been taking oral CPA in Thailand, there have been reports that oral CPA is not very effective for severe HSPN [15]. In addition, a randomized-controlled trial about IVCY demonstrated that the addition of cyclophosphamide to steroid administration provides no benefit compared with steroid administration alone [16]. On the other hand, there have been a few reports that IVCY is effective for severe HSPN [17, 18]. In fact, IVCY is effective for other types of systemic vasculitis, such as lupus nephritis and Wegener granulomatosis, with renal involvement. IVCY is as effective as oral CPA, and the side effects of IVCY are fewer than those of oral CPA [19].

As far as we know, only two reports have discussed the use of IVCY for HSPN [17, 18]. One of them reported the curative effect of IVCY in Japanese with an English abstract [17]; therefore, the details are not available in English. The other was a case report in English describing 3 patients with HSPN [18]; however, that report is not useful for clinical practice, because it did not report any details. The Cr level was not given in the first case. In the second case, the patient's renal function and hematuria seemed to be restored, but kidney biopsy was not performed. In the third case, urinary test results were not given, although renal pathology was evaluated and essential data, such as Cr, were collected.

In consideration of the above two reports, which were incomplete, the present report is the first credible case report in English about the use of IVCY for severe HSPN. The patient's Cr level had risen to more than 5 mg/dL at first, but, interestingly, his Cr level improved to 1.6 mg/dL after IVCY, while we treated him. Based on our experience with the present case, IVCY was so effective for severe HSPN that IVCY might be the first choice for future such cases. However, we cannot deny racial differences in the clinical effects of IVCY and steroid-pulse therapy for HSPN between Caucasians and the Japanese. In general, CPA is used for severe nephrotic syndrome. CPA has been reported to be effective for membranous nephropathy (MN) in Western countries, but in Japan, CPA is not effective and steroid therapy is the most effective for MN [20, 21]. Therefore, the results of the present case suggest that IVCY would be preferable over steroid-pulse therapy to treat severe HSPN with nephrotic syndrome in Caucasian patients.

Among 250 adults with HSPN who were retrospectively analyzed for a median of almost 15 years, 11 % of the patients became dialysis dependent [6]. An additional 27 % had a creatinine clearance <50 mL/min (half were <30 mL/min). Transplantation is also a treatment option, although HSPN recurs in 35 % of recipients, with graft loss

in 11 % of patients within 5 years from transplantation [6]. Considering the clinical presentation and ISKDC grade in a previous report of severe HSPN [24], which found that 35 % of children with HSPN symptoms (nephritis or nephrosis) lasting more than 1 month and ISKDC $\geq$ III developed active renal disease (25 %) and end-stage renal disease (10 %), our patient's kidney prognosis might not be very good, even though his urine abnormality and creatinine level improved.

Conclusion

We experienced severe steroid-resistant HSPN with highly active histological findings in a 37-year-old Canadian man. The patient's renal function and urine protein markedly improved with IVCY without serious side effects. This outcome suggests that IVCY might be an effective therapy for severe HSPN.

Compliance with ethical standards

Conflict of interest The authors have declared that no conflict of interest exists.

Informed consent Written informed consent was obtained from the patient for the publication of this case report and accompanying images.

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