Effects of Cyclophosphamide Pulse Therapy on the Clinical and Histopathological Findings, Particularly Crescent Formation, in a Patient with Adult-onset Steroid-refractory Henoch-Schönlein Purpura Nephritis

Yusuke Tanaka¹, Yuri Nakashima², Toru Mima², Masaki Ohya², Shuto Yamamoto¹, Sou Kobayashi³, Asuka Masumoto², Koji Masumoto⁴, Takuro Yano³, Mari Moribata², Wataru Yoshimoto⁵, Shintaro Yamanaka¹, Daisuke Koreeda², Yoshiyuki Hanba³, Koichi Tatsuta¹, Toshifumi Sakaguchi¹, Shigeo Negi² and Takashi Shigematsu³

Abstract

A 29-year-old woman was diagnosed with Henoch-Schönlein purpura nephritis (HSPN) based on the presence of purpura and histopathological findings showing crescent formation, mesangial proliferation and IgA deposition in the glomerular mesangium. She was treated with high-dose steroids; however, the nephritic syndrome persisted. Therefore, we diagnosed her with steroid-resistant HSPN and decided to add treatment with cyclophosphamide pulse therapy. After one year of treatment, the histopathological findings, including crescent formation and IgA deposition, improved, as confirmed on a renal biopsy, and the patient fulfilled the criteria for complete remission. Cyclophosphamide pulse therapy may be considered an effective treatment for intractable HSPN.

Key words: histopathology, Henoch-Schönlein purpura, glomerular nephritis, renal biopsy


Introduction

Henoch-Schönlein purpura (HSP) is a systemic vasculitis syndrome first reported by Heberden in 1802 (1). One of its characteristic histopathological features is the deposition of immune complexes on target organs, including the skin and glomeruli (2). The clinical features involve petechiae, joint pain, abdominal pain and hematuria, which appear in patients with HSP from the early to late periods during the clinical course. Glomerular nephritis accompanying HSP is called purpura nephritis (HSPN), occurring in approximately 33% of pediatric cases and approximately 63% of adult cases, although many reports show differences in prevalence (3). Moreover, the degree of organ dysfunction tends to be more severe in adults.

Regarding the treatment of HSP, many patients with purpura as the only symptom achieve remission with rest. In contrast, if the patient also shows signs of organ dysfunction, such as renal damage, steroid therapy is recommended (4-6). Patients refractory to steroids may be successfully treated with immunosuppressive agents, as evidenced by alleviation of their clinical symptoms (7-14); however, to our knowledge, there are few reports of the findings of histopathological evaluations of the effectiveness of immunosuppressive therapy for HSPN.

We herein report that the administration of cyclophosphamide pulse therapy, an immunosuppressive treatment, improved both the clinical symptoms and histopathological findings in an adult HSPN patient with steroid-resistant...
A 29-year-old Japanese woman developed muscle pain and edema of the lower legs in January 2010. When these symptoms did not improve after a few weeks, the patient visited a dermatologist, who diagnosed her with allergic purpura and referred her to a physician. In March 2010, the patient visited a dermatologist, who diagnosed her with allergic purpura and edema with purpura on the legs. When the patient was admitted to the hospital for an intensive examination, including a renal biopsy and treatment.

A histopathological examination of the biopsy specimen obtained before and after the administration of cyclophosphamide pulse therapy in the current patient with Henoch-Schönlein purpura nephritis refractory to steroid treatment was performed. (A, B) A low-power examination of the first and second renal biopsy specimens, respectively [Periodic acid-Schiff (PAS) staining, ×40]. (C, D) Higher magnification of the first and second renal biopsy specimens, respectively (PAS staining, ×200). (E, F) Immunofluorescence examination with anti-human IgA antibodies in the first and second renal biopsy specimens, respectively.

Case Report

A 29-year-old Japanese woman developed muscle pain and edema of the lower legs in January 2010. When these symptoms did not improve after a few weeks, the patient visited a dermatologist, who diagnosed her with allergic purpura and referred her to a physician. In March 2010, she experienced abdominal pain, and evidence of stomach ulcers was noted on esophagogastroduodenoscopy. Thereafter, a gradual increase was detected in the levels of proteinuria and hematuria, with accompanying casts and a decrease in the concentration of serum albumin, which suggested a diagnosis of HSPN. At the beginning of June, she was admitted to the hospital for an intensive examination, including a renal biopsy and treatment.

On a physical examination, the patient displayed purpura and edema of the lower legs, although no abnormalities of the mouth, chest, abdomen, joints or nervous system were observed. Her blood pressure was in the normal range at 116/68 mmHg. However, a urinalysis revealed massive proteinuria (2.8 g/day) and hematuria (>100 red blood cells (RBC) per high-power field (HPF)) and white blood cells (5-9/HPF), and a biochemical examination showed a remarkably decreased serum concentration of albumin (2.8 g/dL) and increased serum concentration of cholesterol (217 mg/dL). Taken together, these findings indicated that the patient was clinically nephrotic, although the level of proteinuria was less than 3.5 g/day. Autoantibodies, including antinuclear antibodies (ANA) and antineutrophil cytoplasmic antibodies (ANCA), were negative, the serum concentration of complement was not decreased (CH50: 41 IU/mL, C3: 108 ng/dL, C4: 25 ng/dL) and no immunoglobulin abnormalities, such as an increased serum concentration of IgA (162 mg/dL), were identified. Furthermore, no cryoglobulin or infectious agents, such as hepatitis virus, were detected, and the coagulation data were within the normal ranges. Therefore, a diagnosis of purpura nephritis was suspected, and a renal biopsy was performed.

A histopathological examination of the biopsy specimen showed 10 glomeruli with no evidence of global sclerosis, although crescent formation was observed in 5/10 glomeruli (two glomeruli with cellular crescents, three glomeruli with fibrocellular crescents) (Fig. 1A, C). Mild mesangial proliferation and expansion were also seen in 1/10 glomeruli, and the extent of endocapillary hypercellularity was severe. Moreover, mild expansion was noted in 10% of the interstitium, in association with tubular atrophy, and immunofluorescence microscopy revealed granular deposits of IgA in the glomerular mesangium (Fig. 1E) and deposits of both C3 and IgM in the mesangium. Electron-dense deposits were also present in the mesangial and paramesangial regions, typical findings for IgA nephropathy and HSPN (Fig. 2). Based on these findings, she was diagnosed as having purpura nephritis (ISKCD category: Class IV).

The patient was subsequently treated with methylprednisolone pulse therapy (1 g/day ×3 days) followed by maintenance treatment with prednisolone (40 mg/day) for five weeks due to the presence of massive proteinuria and hypoaubuminemia. Although the clinical symptoms of edema and purpura of the legs were ameliorated, little improvement was observed in the proteinuria (3.5 g/day), and the diagnosis was changed to steroid-resistant nephrotic syndrome. We also decided to add treatment with cyclophosphamide pulse...
therapy (1 g/month) due to the detection of many glomeruli with crescent formation, similar to the features of crescentic glomerular nephritis in cases of microscopic polyangiitis. Because cyclophosphamide is a slow-acting drug that requires several months of treatment to achieve an improvement in proteinuria, the patient was discharged from the hospital in August 2010. Unfortunately, no assessments of the proteinuria were performed for six months because, each month, the patient was menstruating at the time of administration of cyclophosphamide pulse therapy. However, because the serum concentrations of both albumin and protein gradually improved (albumin: 4.0 g/dL, total protein: 6.3 g/dL), the combination treatment was judged to be effective and continued monthly for six months, followed by bi-monthly for the next six months (Fig. 3). The level of hematuria decreased after the first round of pulse therapy from >100 RBC/HPF to 1-4 RBC/HPF, and no adverse effects of either bone marrow suppression, such as neutropenia below 4,000/μL, or infection were seen during the course of cyclophosphamide pulse therapy. The dose of oral prednisolone was gradually reduced and continued, and the patient achieved partial remission in May 2011.

A repeat biopsy was performed to evaluate the treatment efficacy in August 2011, after the ninth round of cyclophosphamide pulse therapy. The histopathological examination showed mild mesangial proliferation and expansion in almost all of 19 glomeruli; however, no evidence of global sclerosis was detected. Although crescent formation was observed in 2/19 glomeruli (one glomerulus with cellular crescents, one glomerulus with fibrocellular crescents) (Fig. 1B, D), the mild expansion in the interstitium with tubular atrophy noted on the previous biopsy had disappeared. In addition, the extent of granular deposition of IgA and IgM identified in the glomerular mesangium was lower than that seen on the first immunofluorescence examination (Fig. 1F), and the endocapillary hypercellularity had improved. These findings suggested that the cyclophosphamide pulse therapy had dramatically ameliorated the nephritis with regard to both the patient's clinical symptoms and histopathological findings (from Class IV on the first renal biopsy to Class III on the second renal biopsy). Because the improvement was confirmed on histopathology, the dose of prednisolone was reduced to 5 mg, without the further administration of any immunosuppressive drugs. In July 2013, the patient fulfilled the criteria for complete remission.

### Discussion

HSPN is considered to have a good prognosis in the short term. In a previous report, 93.9% of pediatric patients and 89.2% of adult patients achieved complete remission (14). On the other hand, the long-term prognosis is not always strong, especially in cases of adult onset (15, 16). A survival rate of 74% and complete remission rate of only 20% over a median observation period of 15 years were reported by Sherestha et al. (17). Regarding markers of renal dysfunction in patients with HPSN, the severity of histopathological changes, such as the degree of crescent formation and interstitial fibrosis, has prognostic importance (17, 18). Moreover, Bogdanović et al. reported that the prognosis is poor among patients with chronic proteinuria greater than 1 g/day and/or those who fulfill the criteria for nephrotic syndrome (17, 19). Therefore, treatment selection should be performed based on the complete clearance of proteinuria or at least a reduction to less than 1 g/day. In the present patient, high-dose steroid therapy was initially selected due to the massive proteinuria; however, it was ineffective and we therefore determined that additional immunosuppressive drugs were required. Patients refractory to steroid therapy are often treated with immunosuppressive agents, such as azathioprine, cyclosporin A and cyclophosphamide. However, protocol for choosing between these agents have not been clarified. In patients with a desire to have children, it may be better to choose azathioprine or cyclosporin A. On the other hand, patients with crescentic glomerular nephritis resembling that observed in cases of microscopic polyangiitis should be treated with cyclophosphamide. Therefore, cyclophosphamide is considered to be indicated for patients with crescentic glomerular nephritis who do not have a desire to have children. The current patient had crescentic glomerular nephritis and no desire to have further children. Hence, we chose cyclophosphamide in this case. Although we do not believe that all patients with HSPN require intravenous cyclophosphamide therapy, as described in a previous report (20), additional treatment with immunosuppressive agents may be needed in cases of steroid-resistant HSPN, especially in patients with crescentic glomerular nephritis, which rapidly decreases the kidney function. In the present case, we diagnosed the patient with steroid-resistant HSPN at five weeks after the start of steroid treatment and added cyclophosphamide pulse therapy before her renal function worsened. Thereafter, her renal function remained stable, with a serum creatinine level of 0.6 mg/dL during the course of treatment. Regarding the dose of cyclophosphamide, 1 g is thought to be too high in Japanese woman. However, the patient’s body surface area was 1.52 m² and
the dose applied in this study was 652 mg/m², similar to that used in a previous report (20). After receiving cyclophosphamide pulse therapy for one year, the patient achieved clinical remission, as confirmed pathologically on the repeat renal biopsy.

In clinical practice, renal biopsies are performed to obtain a definitive diagnosis, although they are rarely used to evaluate therapeutic efficacy. Therefore, reducing or discontinuing the dose of steroids or immunosuppressive drugs is often planned without knowing whether the nephritis has improved pathologically. As a result, relapse may occur in patients who appear to have fulfilled the criteria for complete remission, which may account for why the rate of complete remission is lower in the long term than in the short term. Because the current patient had crescentic glomerular nephritis, which may rapidly lead to renal failure, we determined whether additional drugs were needed after administering treatment with cyclophosphamide pulse therapy for one year and subsequently performed a repeat renal biopsy. Repeat renal biopsies are useful for assessing whether additional treatment is required or whether the patient has a risk of relapse or worsening of their condition, such as that associated with persistent hematuria or proteinuria greater than 1 g/day. Therefore, the levels of hematuria and proteinuria are potential candidate surrogate markers for evaluating the therapeutic efficacy. Moreover, performing additional renal biopsies enables an examination of the relationship between clinical and pathological improvements.

In the current case, the steroid-resistant HSPN improved both clinically and pathologically following the administration of cyclophosphamide pulse therapy. Moreover, by checking for a pathological improvement, we were able to reduce the dose of steroids without inducing recurrence of the nephritis. The following two mechanisms accounting for the improvement in crescent formation achieved with cyclophosphamide pulse therapy in this patient can be speculated: 1. the deposition of IgA in the mesangium was reduced by a decrease in the production of IgA as a result of suppression of the B cell activity caused by the therapy and 2. suppression of the fibroblast or myofibroblast activity by this therapy reduced the extent of fibrosis in the glomeruli (21, 22).

This is the first report of the use of cyclophosphamide pulse therapy to successfully improve both clinical symptoms and histopathological changes, such as crescent formation in the glomeruli, in a patient with HPSN. This case suggests that cyclophosphamide pulse therapy is effective for steroid-resistant HSPN and that repeat renal biopsies are useful for evaluating the treatment efficacy.

The authors state that they have no Conflict of Interest (COI).

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