Successful Treatment of Progressive Henoch-Schönlein Purpura Nephritis with Tonsillectomy and Steroid Pulse Therapy

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Abstract

Henoch-Schönlein purpura (HSP) is a systemic disorder characterized by a leukocytoclastic vasculitis involving small vessels with the deposition of IgA immune complexes. The renal involvement is the major cause of morbidity and mortality in patients with HSP. We report here an adult patient with HSP nephritis (HSPN) accompanied by persistent proteinuria and progressive renal dysfunction despite conventional therapy. The patient was successfully treated with tonsillectomy followed by intravenous pulse methylprednisolone and oral prednisone. The combination therapy resulted in a significant decrease in proteinuria, improvement of renal function and the disappearance of microhematuria. The patient finally reached a stage of clinical remission.

Key words: proteinuria, hematuria, tonsil, IgA, prednisolone, remission

Introduction

Henoch-Schönlein purpura (HSP) is a systemic vascular disease histopathologically characterized by a leukocytoclastic vasculitis involving small vessels with the deposition of immunoglobulin A (IgA) immune complexes (1–3). It is a multi-system disorder mainly affecting the skin, joints, gastrointestinal tract, and kidneys. The renal involvement is the major cause of morbidity and mortality in patients with HSP. HSP preferentially affects children between the ages of 5 and 15 years and also occurs in adults (4, 5). A few patients develop persistent proteinuria and subsequent end-stage renal failure. Indeed, as indicated in a recent report, the clinical presentation of HSP nephritis (HSPN) in adults is more severe and its outcome worse than in children (6).

The pathogenesis of HSP and HSPN remains unknown. Increased polymeric IgA production by the mucosal immune system including the tonsils, intestine, and skin in response to certain antigens has been hypothesized as a potential mechanism for the development of the disease. It has been suggested that HSPN and IgA nephropathy represent a spectrum of clinical presentations of similar disorders (3). The granular IgA and C3 immune deposits found predominantly in the mesangium are indistinguishable from those seen in IgA nephropathy (3). Frequent association between upper respiratory tract infection and the development of HSP is also suggested (3).

In patients with HSPN, no study has yet been able to demonstrate the ability of any treatment to completely prevent the progression to end-stage renal failure. Methylprednisolone pulse therapy alone does not induce complete remission in all HSPN patients. Approximately 20% of the treated patients exhibit persistent nephropathy or progressive end-stage renal failure despite treatment with this monotherapy (7). Recent reports have shown that tonsillectomy and high-dose methylprednisolone pulse therapy together have a significant impact on clinical remission in patients with IgA nephropathy (8). We report here an adult patient with HSPN accompanied by persistent proteinuria and progressive renal dysfunction regardless of conventional therapy, who was successfully treated with tonsillectomy followed by intravenous pulse methylprednisolone and oral prednisone. This combination therapy resulted in a significant decrease in...
proteinuria, an improvement of renal function and the disappearance of microhematuria. The patient finally did achieve clinical remission.

**Case Report**

A 25-year-old Japanese man was admitted to our hospital because of proteinuria, microhematuria, and renal dysfunction. In 1989, he had received a diagnosis of Henoch-Schönlein purpura nephritis, the signs having been purpura on his lower legs, abdominal pain, gross hematuria, and arthralgias. He took an anti-platelet agent, dipyridamole, for the nephritis. Two years later, a second renal biopsy was performed because of persistent proteinuria and microhematuria; the histology revealed diffuse mesangial proliferative glomerulonephritis. Prednisone, azathioprine, and dipyridamole were prescribed but were then discontinued a few months later because of nausea and vomiting. He took enalapril because of an elevation of blood pressure to 140/90 mmHg. In 1995, a third renal biopsy was performed; the histology on this occasion revealed there had been a progression of glomerulonephritis. Treatment with prednisone (50 mg daily), warfarin, and dipyridamole was started but the urinary abnormalities continued. Two years later, a forth renal biopsy was done; glomerular sclerosis and interstitial fibrosis with tubular atrophy had developed. Prednisone was discontinued and the patient took enalapril maleate (5 mg daily) and dipyridamole after that. Three weeks before admission, the daily proteinuria had increased to 4.8 g.

On admission, the temperature was 36.8°C, the pulse 72, and the respirations 20. The blood pressure was 128/84 mmHg. On physical examination, the patient had no discernable purpura or rash. The lung and heart sounds were normal. Abdominal examination revealed no tenderness. There was no peripheral edema or evidence of active synovitis. A neurologic examination revealed no abnormalities. The patient was mildly obese (body mass index, 25.7). He had a past history of having several upper respiratory tract infections a year. His father was receiving maintenance treatment with prednisone (50 mg daily), azathioprine, and dipyridamole was started but were then discontinued a few months later because of nausea and vomiting. He took enalapril because of an elevation of blood pressure to 140/90 mmHg. In 1995, a third renal biopsy was performed; the histology on this occasion revealed there had been a progression of glomerulonephritis. Treatment with prednisone (50 mg daily), warfarin, and dipyridamole was started but the urinary abnormalities continued. Two years later, a forth renal biopsy was done; glomerular sclerosis and interstitial fibrosis with tubular atrophy had developed. Prednisone was discontinued and the patient took enalapril maleate (5 mg daily) and dipyridamole after that. Three weeks before admission, the daily proteinuria had increased to 4.8 g.

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His urine was positive (++) for protein; the sediment contained 5 to 10 red blood cells per high-power field, with a granular cast. The following serologic values were obtained: total protein, 6.28 g/dl (62.8 g/l); albumin, 3.31 g/dl (33.1 g/l); total cholesterol, 271 mg/dl (7.01 mmol/l); creatinine, 1.17 mg/dl (104 µmol/l); urea nitrogen, 15.0 mg/dl (5.3 mmol/l); uric acid 9.6 mg/dl (normal range 2.4 to 5.7 mg/dl). Creatinine clearance was 56.0 ml/min (0.93 ml/s), and the urine volume 1,800 ml/day. The level of serum IgG was 1,040 mg/dl (normal range, 870 to 1,818; 8.81 g/l); IgA, 419 mg/dl (normal range, 110 to 424; 4.19 g/l); and IgM, 55 mg/dl (normal range, 31 to 252; 0.55 g/l). The patient had no anemia or leukocytosis. Negative tests were obtained for antinuclear antibody, rheumatoid factor, cryoglobulin, hepatitis B surface antigen and antibody, and hepatitis C antibody. Serum complement, prothrombin time, activated partial thromboplastin time, and factor XIII levels were all normal.

To evaluate the renal involvement, percutaneous renal biopsy was performed on hospitalization day 3. Immunofluorescent studies indicated an intense granular deposition of IgA and C3 predominantly in the glomerular mesangium. A moderate deposition of IgG and a mild deposition of IgM and fibrin were also observed. The complement C1q was not detected in the glomeruli. On light microscopy, five of six glomeruli observed showed mild, focal and segmental mesangial proliferation (Fig. 1A). Fibrous adhesion of Bowman’s capsule was noted in three glomeruli. One instance of advanced global sclerosis was observed. There was a fibrocellular crescent formation in one glomerulus. The renal interstitium exhibited focal and moderate fibrosis accompanied by tubular atrophy and cell infiltration (Fig. 1A). The renal arterioles were found to have undergone mild arteriolar sclerotic changes. The tubulointerstitial changes were worse than those found on the fourth renal biopsy four years previously.

One month after the renal biopsy, the patient underwent tonsillec-tomy. Both tonsils were moderately hypertrophied. The resected tonsils displayed lymphoid hyperplasia, and distension of the crypts containing keratin plugs, which resulted from keratinization and desquamation of the lining epithelium (Fig. 1B). Large colonies of cocci had formed, particularly in the deep parts of the crypts (Fig. 1C). The parenchyma of the tonsils exhibited mild fibrosis. These findings indicate the presence of chronic tonsillitis. High-dose methylprednisolone therapy (0.5 g/d for 3 days for three courses) was started two weeks after tonsillec-tomy, followed by oral prednisolone at an initial dose of 0.6 mg/kg on alternate days (Fig. 2). The oral prednisolone was tapered gradually over 1 year. Antiplatelet drugs (dipyridamole, 300 mg/d) and enalapril (5 mg/d) were also administered. Three months later, the daily proteinuria had decreased to 1.0 g and the sediment contained only 2 to 3 red blood cells per high-power field and without a granular cast. Creatinine clearance increased to 95.7 ml/min (1.60 ml/s) and serum creatinine decreased to 0.82 mg/dl (72.8 µmol/l). After six months, the daily proteinuria was 0.4 g/d and no microhematuria was observed. The level of serum IgA decreased to 91.4 mg/dl (0.91 g/l). There were no purpuric rashes, arthralgias or abdominal symptoms during the course of the therapy.

**Discussion**

Although the disease is usually self-limited with a good eventual outcome, a certain population of patients with HSPN are reported to develop renal failure (2, 5–7). Therefore, persistent proteinuria and progressive renal dysfunction in patients with HSPN should be considered as a potential target for aggressive treatment.

There is evidence that corticosteroids increase the rate of resolution of both arthritis and abdominal pain in HSP;
however, the treatment of active and progressive renal disease should be considered as a separate issue in this illness. At present there are no controlled trials of steroid pulse therapy in patients with HSPN. Niaudet and Habib reported a prospective study of the treatment of severe forms of childhood HSPN and evaluated the effects of intravenous methylprednisolone pulse therapy (3 days) followed by oral prednisone (3.5 months) on the outcome of the nephropathy (7). The study reported that 30 of 38 children had clinically recovered or exhibited only minimal urinary abnormalities, but 4 still had persistent nephropathy and 4 had in fact progressed to end-stage renal failure. Other regimens include azathioprine and daily oral prednisone or intravenous methylprednisolone followed by azathioprine and alternate-day prednisone for a mean of 15 months (9) and multidrug studies such as intravenous pulse methylprednisolone (3 days), oral cyclophosphamide (2 months), dipyridamole (6 months) and oral prednisone (3 months) (10). In the former study, 2 of 21 children progressed to end-stage renal failure (9) and in the latter 4 of 12 patients evidenced partial remission, one of whom had decreased renal function (10). These
regimens are aimed at reversing the inflammatory responses such as mesangial proliferation and macrophage infiltration rather than the IgA deposition in the glomerulus *per se*.

Both an increased synthesis and a diminished clearance of IgA have been implicated in the pathogenesis of IgA immune complex deposition. Increased polymeric IgA production by the mucosal immune system in response to a mucosally presented antigen has been hypothesized to be a mechanism for the development of HSP (3, 11, 12). IgA is the main immunoglobulin directed against external viral and bacterial antigens. There is frequent association between upper-respiratory tract infection and the development of HSP (3). Therefore it has been suggested that certain viral or bacterial infections may cause HSPN as the result of the deposition of the IgA immune complex produced in response to antigens (13). Considerable efforts have been directed toward the search for antigens involved in the disease but only limited success has been achieved to date. A few antigens have been positively identified to have diffuse and global distribution in glomeruli in patients with HSPN. Recently, however, Ogura et al reported diffuse global staining of the mesangium with antiserum to *Haemophilus parainfluenzae* in one-third of their patients with HSPN and IgA nephropathy (14). Masuda et al have also reported that nephritis-associated plasmin receptor, a group A streptococcal antigen, is found in the glomerular mesangium in patients with HSPN after streptococcal infection (15).

Tonsils play a role in the mucosal immune defense against viral and bacterial antigens. Previous studies have suggested that the tonsils are closely related to HSPN as well as IgA nephropathy. Currently there are few reports focusing on the effect of tonsillectomy on patients with HSPN, particularly in Japan (16, 17). Three of 5 patients with HSPN reportedly showed a decrease in both hematuria and proteinuria after tonsillectomy. However, 3 of 6 with HSPN also improved without tonsillectomy in that study (17). The clinical benefit of tonsillectomy alone or in combination with other therapies in patients with IgA nephropathy remains controversial (18, 19). Hotta et al recently reported that tonsillectomy and intravenous methylprednisolone pulse therapy (3 days for three courses) followed by oral prednisolone for over a year significantly impacted clinical remission in Japanese patients with IgA nephropathy (8). Tonsillectomy may lead to the removal of a pharyngeal infectious focus, as shown in Fig. 1B and C, and thus the disappearance of the lymphoid tissue which had been actively recruiting the activated IgA-producing cells. This effect could partly explain the significantly decrease in serum IgA level seen in the present patient.

Since HSP predominantly affects children and the clinical course of the disease is often self-limiting, tonsillectomy may not be optimal for childhood patients with HSPN. The incidence of HSPN and the severity of its clinical manifestations in adults appear not to be the same as in children (6). Persistent proteinuria and chronic progressive renal dysfunction should be taken to be a therapeutic target in adulthood patients with HSPN. Tonsillectomy combined with subsequent pulse steroids may be one of the therapeutic strategies deserving consideration for such patients. Although randomized prospective controlled trials are very important, a randomized control study of a surgical operation such as a tonsillectomy is extremely hard to practically carry out. As a consequence, no information has been made available worldwide about the clinical efficacy of tonsillectomy on the long-term renal survival of patients with HSPN as compared to those with IgA nephropathy (18, 19). Nevertheless, we propose that a combination therapy of tonsillectomy along with steroid pulse therapy should be considered in adult patients with severe HSPN exhibiting persistent proteinuria and chronic progressive renal dysfunction.

**References**
