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Successful therapy with tonsillectomy plus pulse therapy for the relapse of pediatric IgA nephropathy treated with multi-drugs combination therapy

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Abstract
Immunoglobulin A nephropathy (IgAN) is the most common form of chronic glomerulonephritis worldwide. In Japan, the treatment for use as an initial therapy was established in Guidelines for the Treatment of Childhood IgA nephropathy; however, no rescue therapy for recurrent or steroid-resistant pediatric IgAN was established. We report here a 15-year-old boy with severe IgAN, who was treated with combination therapy involving prednisolone, mizoribine, warfarin, and dilazep dihydrochloride for 2 years. The response to the combination therapy was good and both proteinuria and hematuria disappeared. The pathological findings at the second renal biopsy were improved and PSL was discontinued. However, due to nonadherence to the treatment regimen and tonsillitis, macrohematuria and an increase of proteinuria were again observed and the pathological findings at the third renal biopsy showed clear deterioration. The patient was, therefore, diagnosed with recurrent IgAN. Tonsillectomy plus methylprednisolone pulse therapy (TMP) was performed as a rescue therapy for the recurrence of severe IgAN. Both the proteinuria or hematuria subsequently disappeared, and no proteinuria or hematuria has been observed and kidney function has remained normal during a 5-year follow-up. The patient experienced no severe side effects associated with the drug regimens. In conclusion, our case suggests that TMP may be an effective and useful rescue therapy for recurrent IgAN after multi-drug combination therapy.

Key words: IgA nephropathy, tonsillectomy plus pulse therapy, recurrence, multi-drugs combination therapy, Mizoribine

Introduction
Primary immunoglobulin A nephropathy (IgAN) is characterized clinically by microhematuria and proteinuria, and histologically by the deposition of immunoglobulin A. IgAN is the most common form of chronic glomerulonephritis worldwide, and progresses to end-stage renal failure in up to 3-15% of pediatric patients. Although the pathogenesis of IgAN has not yet been fully characterized, it has been postulated that the associated glomerular damage occurs as a result of the deposition of IgA-containing immune complexes. In many centers, immunosuppression, particularly with combination therapy, for 2 years is reserved for severe cases categorized as crescentic nephritis. Recently, in Japan, Kamei et al. reported that 90% of children with severe IgAN treated with combination therapy, consisting of prednisolone, heparin-warfarin, dipyriramole, and mizoribine or azathioprine, had no or only mild proteinuria, and mentioned that combination therapy had improved the long-term outcome of IgAN. The prognosis of most severe cases of pediatric IgAN treated with multi-drugs combination therapy is good; however, some patients with severe IgAN experience recurrence after combination therapy or resistance to treatment. We also showed that 11% of children with severe IgAN treat-
ed with combination therapy, consisting of prednisolone, mizoribine, warfarin, and dipyridamole, had the relapse of IgAN\textsuperscript{10}, and there have been few reports on adequate treatments for these IgAN patients.

On the other hand, there have been some reports on the efficacy of tonsillectomy for IgAN in adult patients\textsuperscript{11-15}. Hotta et al. initially described tonsillectomy plus methylprednisolone pulse therapy (TMP), which then became a popular approach to treating IgAN for several years in Japan\textsuperscript{11}. A retrospective analysis showed that approximately 60% of their patients who underwent TMP achieved remission of urinary abnormalities.

We here report a child with severe IgAN who experienced recurrence of the disease after multidrug combination therapy and who was subsequently successfully treated with TMP.

**Case**

Proteinuria and hematuria were detected by a family doctor after the patient had presented with a common cold at fifteen years old. The patient was referred to our hospital and admitted. Laboratory tests revealed a leukocyte count of 7,600/mm\(^3\), erythrocyte count of \(430 \times 10^4/mm^3\), platelet count of \(26.5 \times 10^5/mm^3\), a serum total protein level of 7.0 g/dl, serum albumin of 4.1 g/dl, serum creatinine of 0.8 mg/dl, and serum total cholesterol of 153 mg/dl. Urinalysis revealed protein excretion of 1.1 g/day, with sediment containing 20-30 erythrocytes, 3-5 leukocytes, and 2-4 granular casts per high-power field. Creatinine clearance (24-h) was 132 ml/min per 1.73 m\(^2\). Immunology studies revealed a C3 of 107 mg/dl, C4 of 13 mg/dl, CH50 of 32.5 U/ml, antinuclear antibody titer of <80 X, negativity for anti-DNA antibodies, and negativity for titers of serum anti-neutrophil cytoplasmic antibodies. Prothrombin time and activated partial thromboplastin time were normal.

The clinical course of our patient is shown in Fig. 1. At day 10 of hospitalization, urinary protein excretion was 1.0 g, and a first renal biopsy was performed. Immunofluorescence microscopic examination revealed predominant IgA and C3 deposits in the mesangial area. Light microscopic examination showed diffuse mesangial proliferative glomerulonephritis with mesangial cell proliferation and moderate mesangial matrix accumulation with cellular crescent and no necrotic lesions (Fig. 2-A).

![Fig. 1. The clinical course of our patient](image-url)
Further, tubular atrophy/interstitial fibrosis were found in about 10% of interstitial lesions. Eighteen of 30 glomeruli showed cellular crescent formation. The patient was, therefore, diagnosed with severe IgAN and was treated with multiple-drug combination therapy that included prednisolone, mizoribine (MZB), warfarin and dilazep dihydrochloride. After treatment, his proteinuria began to gradually decrease. During the tapering off of the PSL treatment, urinary protein excretion decreased. At 4 months after the onset of treatment, the proteinuria and hematuria had disappeared, and a second renal biopsy was performed to investigate the efficacy of treatment at 24 months after treatment. Immunofluorescence microscopic examination revealed a small degree of IgA deposition in the mesangial area. Light microscopic examination revealed slightly segmental mesangial cell proliferation and mesangial matrix accumulation, although only one of 26 glomeruli showed fibro-crescent formation, with only one other glomerulus showing global sclerosis (Fig. 2-B). Thus, the administration of PSL was discontinued. At 2 months after the discontinuation of PSL, microhema turia and proteinuria reappeared. Thereafter, he did not visit our hospital due to his busy schedule. Macrohema turia appeared concomitantly with an episode of tonsillitis, and he was again referred to our hospital and admitted. He demonstrated swelling of the tonsils, but no edema. Urinary protein excretion was 1.9 g/day, and a third renal biopsy was performed. Immunofluorescence microscopic examination revealed predominant IgA and C3 depositions in the mesangial area. Light microscopic examination showed diffuse mesangial proliferative glomerulonephritis with mesangial cell proliferation and moderate mesangial matrix accumulation, with tubular atrophy/interstitial fibrosis observed in about 30% of interstitial lesions (Fig. 2-C). Four of 18 glomeruli showed global sclerosis and one showed fibro-cres-

![Image](https://via.placeholder.com/150)

**Fig. 2.** The pathological findings of our patient
A: Light microscopic examination at the time of first renal biopsy showed diffuse mesangial proliferative glomerulonephritis with mesangial cell proliferation and moderate mesangial matrix accumulation with cellular crescent (PAM stain ×400).
B: Light microscopic examination at the time of second renal biopsy revealed slightly segmental mesangial cell proliferation and mesangial matrix accumulation (PAS stain ×400).
C: Light microscopic examination at the time of third renal biopsy revealed glomeruli showing mesangial proliferative glomerulonephritis with mesangial cell proliferation and moderate mesangial matrix accumulation, and numerous inflammatory cells were found around the glomeruli (PAS stain ×200).
IgAN is characterized clinically by microhematuria and proteinuria, and histologically by the deposition of immunoglobulin A. Under pathological conditions, O-linked carbohydrates in the hinge region of the IgA1 molecule are under-galactosylated, and defective IgA1 forms circulating or in situ immunecomplexes. The subsequent deposition of these immune complexes within the mesangium plays a key role in the pathogenesis of IgAN2).

In Japan, according to the “Guidelines for the treatment of childhood IgA nephropathy” published by the Japanese Society for Pediatric Nephrology, children with IgAN are divided into two categories based on disease severity; i.e., mild and severe IgAN5). Severe and mild cases were defined as patients who meet the respective criteria for ‘clinical findings’ or ‘histological findings’. In severe cases, the ‘clinical findings’ consisted of heavy proteinuria (an early morning urinary protein to creatinine ratio >1.0), and ‘histological findings’ involved cases with >80% of glomeruli showing moderate or severe mesangial cell proliferation, crescent formation, adhesion, or sclerosis or cases with >30% of glomeruli showing crescent formation. In our case, we diagnosed the patient with severe IgAN based on the heavy proteinuria and typical pathological findings of IgAN.

According to the “Guidelines for the treatment of childhood IgA nephropathy” the recommended treatment for severe IgAN is combination therapy consisting of prednisolone, warfarin, dilazep dihydrochloride, mizoribine or azathiopurine for 2 years16). To date, there have been only a few reports on this combination therapy. Yoshikawa et al. reported the beneficial effects of multiple-drug therapy consisting of prednisolone, azathioprine, heparin–warfarin, and dipyridamole in severe pediatric IgAN5), and we previously reported that prednisolone, warfarin, and dipyridamole therapy combined with mizoribine was effective in ameliorating proteinuria and histological severity in IgAN children at both short- and long-term follow-up8–10). For this reason, the current case received combination therapy of prednisolone, mizoribine, warfarin, and dilazep dihydrochloride for 2 years as an initial therapy. The response to the combination therapy was good and the proteinuria and hematuria both disappeared. The pathological findings at the second renal biopsy were also improved. However, after the discontinuation of PSL, a combination of nonadherence to the treatment regimen and tonsillitis led to the appearance of macrohematuria and an increase in proteinuria. The pathological findings at the third renal biopsy showed clear deterioration and the patient was, therefore, diagnosed with recurrent IgAN.

We performed TMP as rescue therapy for this recurrence of IgAN. To date, the “Guidelines for the treatment of childhood IgA nephropathy” have not contained any recommendations regarding treatment for recurrences of severe IgAN. In our patient, both the proteinuria and hematuria disappeared after TMP; and no proteinuria or hematuria has been observed and renal function has remained normal during a 5-year follow-up. The patient did not experience any severe side effects associated with the drug regimens. Furthermore, we think that TMP may be effective for recurrent IgAN as well as safe for children in comparison with multidrug combination therapy as TMP does not use immunosuppressive drugs other than PSL such as azathioprine, mizoribine and cyclophosphamide.

As to long-term follow-up studies on multidrug combination therapy for severe pediatric IgAN, Kamei et al. reported a marked improvement in renal survival in severe IgAN patients treated with combination therapy7). We also found that 89% of children with severe IgAN treated with combination therapy, consisting of prednisolone, mizoribine, warfarin, and dipyridamole, had no or only mild proteinuria, and reported that combination therapy had improved the long-term outcome of IgAN19). In other words, these findings suggested that few patients...
with persistent nephritis and recurrent IgAN have been included in long-term follow-up studies. Furthermore, there have been few reports on recurrent and steroid-resistant pediatric IgAN, and no rescue therapy for these IgAN patients has been established.

On the other hand, there have been some reports on the efficacy of tonsillectomy or TMP for IgAN in adults and children\(^{11-15}\). Hotta et al. initially described TMP, which then became a popular approach to treating IgAN for several years in Japan. A retrospective analysis showed that approximately 60% of their patients who underwent TMP achieved remission of urinary abnormalities and reported that TMP might be more effective than conventional steroid therapy in patients with a baseline creatinine level of <2 mg/dl. In our report, our patient had normal renal function\(^{11}\). In addition, based on a multivariate analysis, Liu et al. reported that tonsillectomy may induce clinical remission and reduce the rate of progression to end-stage renal disease in patients with IgAN\(^{11,13}\). We also reported that TMP as an initial therapy for pediatric IgAN was effective in a short-term follow-up study\(^{19}\). Our case presented herein further suggest that TMP was effective as a rescue therapy for recurrent severe IgAN after multi-drug combination therapy.

Although the mechanism underlying the favorable effect of TMP on IgAN remains unclear, previous studies have suggested that the tonsils are closely associated with the pathogenesis of IgAN\(^{11-15}\). In our study, the tonsils removed by tonsillectomy showed chronic tonsillitis, and these findings suggest a relationship between the tonsils and IgAN. The following mechanism for the onset and progression of IgAN has been proposed\(^{19}\). The initial phase of pathogenesis involves the continuous antigenic stimulation of the innate immune system by the tonsillar mucosa via the mucosa-bone marrow axis. Thereafter, aberrantly glycosylated IgA1 produced as a result of the anomalously stimulated immune response in the bone marrow is deposited within the mesangial region\(^{19}\). Tonsillectomy might act upstream of the pathogenic mechanism by eliminating antigenic stimuli from the tonsillar mucosa, whereas steroid pulse therapy acts downstream by suppressing the abnormal immune response in the bone marrow and subsequent inflammation in the renal glomeruli. Furthermore, ARB and ACEI might inhibit urinary protein excretion. Our patient demonstrated continued remission for 5 years after TMP. Our rationale for using TMP in cases of IgAN is that steroid pulse therapy and tonsillectomy reduce IgA production and minimize the abnormal immune response and inflammatory events following glomerular IgA deposition.

In conclusion, our case suggests that TMP may be an effective and useful rescue therapy for recurrent IgAN. It is, of course, difficult at this time to emphasize the efficacy of TMP for some patients with recurrent IgAN after combination therapy based on this case a only one patient was examined and the observation period was still short; therefore, further evaluation of the efficacy of this treatment regimen in case-control studies is necessary.

**Conflict of Interest**

We have no conflicting interests affecting the present study.

References

Long prognosis of tonsillectomy plus pulse therapy


