CASE REPORT

IgA Nephropathy and Psoriatic Arthritis that Improved with Steroid Pulse Therapy and Mizoribine in Combination with Treatment for Chronic Tonsillitis and Epipharyngitis

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Abstract

A 65-year-old man was admitted to our hospital with edema and renal dysfunction. He had received a diagnosis of psoriatic arthritis at 50 years of age. As a renal biopsy showed IgA nephropathy (IgAN), bilateral tonsillectomy was performed, and one course of steroid pulse therapy with an oral steroid and mizoribine were subsequently administered. The patient’s proteinuria gradually reduced in association with an improvement in the renal function. In addition, the rash and arthralgia were ameliorated. In this case, adding treatment for chronic epipharyngitis accelerated the curative effects, and focal infection therapy consisting of immunosuppressive drugs was effective for both IgAN and psoriatic arthritis.

Key words: IgA nephropathy, psoriatic arthritis, focal infection treatment

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Introduction

It has been reported that the administration of steroid pulse therapy after bilateral tonsillectomy is effective in cases of IgA nephropathy (IgAN). The palatine tonsils are a central component of the nasopharynx-associated lymphoid tissue (NALT), which forms part of Waldeyer’s tonsillar ring. These tonsils take in antigens invading from the oral and nasal cavities and subsequently form antibodies. It has also been demonstrated that the number of IgA plasma cells is increased in the palatine tonsils in IgAN patients and that IgA1-positive cells are present among the dendritic cells of the tonsillar follicles. In addition, there are many reports suggesting the presence of quantitative and qualitative abnormalities in Galβ1 and 3GalNAc in O-linked glycans in hinge regions. O-glycosylation abnormalities are of particular interest as a principal cause of IgAN (1).

Focal infection is a clinical state in which chronic localized inflammation in one part of the body causes reactive organic or functional disabilities in distal locations. The most frequent site of origin is the tonsils. Typical diseases caused by tonsillar focal infection include orthopedic disorders, such as sternocostoclavicular hyperostosis and reactive arthritis, and cutaneous diseases, such as palmoplantar pustulosis and erythema nodosum, in addition to IgAN and purpura nephritis. Psoriasis may also present with the exacerbation of rashes due to infection of the upper respiratory tract and tonsillitis. Furthermore, it has been widely reported that tonsillectomy is effective for treating tonsillar focal diseases (2).

Psoriatic arthritis is a form of chronic inflammatory arthritis accompanying bone and cartilage lesions, which coexist in 4-30% of psoriasis cases (3). In addition, deformation or articular destruction are observed at five or more locations in 55% of patients whose articular symptoms developed more than 10 years previously. Such patients are treated in accordance with guidelines for rheumatoid arthritis, and the administration of a tumor necrosis factor-alpha (TNF-α) inhibitor is often considered in intractable cases (4).

We experienced a case of IgAN with coexisting psoriatic

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arthritis in which we performed tonsillectomy and administered steroids and mizoribine (MZR) in addition to treatment for the focal infection. Consequently, the patient’s rash, arthralgia and renal function improved and the hematuria completely disappeared.

**Case Report**

A 65-year-old man scheduled for a renal biopsy had been visiting a local doctor for the treatment of psoriatic arthritis since 50 years of age. The psoriatic arthritis was refractory and had been treated with steroids, cyclosporin and vitamin D ointment. The patient reported strong joint pain, and non-steroidal anti-inflammatory drugs (NSAIDs) were used empirically. In addition, he had been prescribed antihypertensives (a calcium channel blocker and angiotensin II receptor blocker) since 60 years of age. Bilateral edema in the lower extremities was observed approximately one month prior to the renal biopsy. A local doctor identified proteinuria and renal function impairment, and the patient was therefore referred to our department for hospitalization. As shown in Fig. 1a, carnation maculae with a scale attached margin were observed across his entire body. Table shows the findings of the laboratory workup performed on admission; anemia and high blood IgA in addition to hematuria, proteinuria and renal function impairment were observed. The renal biopsy, performed the day after admission, showed almost half (of a total of approximately 30) of the glomeruli to be

### Table. Laboratory Data at Admission

<table>
<thead>
<tr>
<th>Peripheral blood</th>
<th>Serological test</th>
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<tbody>
<tr>
<td>WBC 5,900/μL</td>
<td>IgG 1,321 mg/dL</td>
</tr>
<tr>
<td>RBC 397 × 10^6/μL</td>
<td>IgA 648 mg/dL</td>
</tr>
<tr>
<td>Hb 11.4 g/dL</td>
<td>IgM 94 mg/dL</td>
</tr>
<tr>
<td>Hct 35.5 %</td>
<td>CH50 &gt; 60 U/mL</td>
</tr>
<tr>
<td>PIt 25.7 × 10^6/μL</td>
<td>C3 147 mg/dL</td>
</tr>
</tbody>
</table>

Blood chemistry:
- TP 7.4 g/dl
- Alb 3.6 g/dl
- ALT 18 IU/L
- LDH 205 IU/L
- T-Chol 189 mg/dL
- LDL-Chol 111 mg/dL
- TG 155 mg/dL
- UA 7.2 mg/dl
- BUN 31.3 mg/dl
- Cr 1.83 mg/dL
- Na 137 mEq/L
- K 4.2 mEq/L
- Cl 105 mEq/L
- Ca 8.7 mg/dL
- Pi 3.2 mg/dL
- CRP 0.67 mg/dl
- HbA1c(NGSP) 6.1%

Figure 1. Appearance of the skin before and 18 months after tonsillectomy. a: Carnation maculae with a scale attached margin were observed across the patient’s entire body before tonsillectomy. b: The rash nearly disappeared 18 months after tonsillectomy.
closporine was halted after the biopsy, the patient’s serum chronic lesions progressing to IgAN. Active lesions, including small necrotizing lesions, with nese histological grade. This status indicated the presence of the Oxford classification and grade IIIC based on the Japa-
istry showed deposition of IgA and C3 in mesangial areas. Progressed into 30% of the renal cortex. Immunohistochemistry, observed in two glomeruli, and tubulointerstitial lesions had cent, reflecting a chronic lesion. Glomerular adhesion was glomerulus exhibited segmental sclerosis with a fibrous cres-
tome. Furthermore, one glomeruli, and a small necrotizing lesion was evident in one glomerulus, reflecting an active lesion. Furthermore, one glomerulus exhibited segmental sclerosis with a fibrous cres-
ment with inflammatory cell infiltration was noted in two glomeruli [B: Periodic acid-Schiff (PAS) stain, ×800]. Small fibrin exudation was seen in Bowman’s space, possibly associated with a necrotizing glomerular lesion in one glomerulus (C: PAM stain, ×800). On immunohistochemistry, deposition of IgA (arrowheads in D) and C3 (arrowheads in E) was noted in a mesangial granular pattern (D: IgA stain; E: C3 stain; D, E: ×600). On electron microscopy, small electron-dense deposits (arrowheads in F) were evident in paramesangial areas (×5,000).

Figure 2. Findings of the renal biopsy. A total of 30 glomeruli were included in the renal biopsy samples, 16 of which had deteriorated (arrowhead in A) with tubular atrophy in addition to interstitial fibrosis in 30% of the renal cortex [A: Periodic acid methenamine silver (PAM) stain, ×400]. Focal segmental proliferative lesions were noted in five to six glomeruli (arrow in A), and small endocapillary proliferative lesions with inflammatory cell infiltration were evident in two glomeruli [B: Periodic acid-Schiff (PAS) stain, ×800]. Small fibrin exudation was seen in Bowman’s space, possibly associated with a necrotizing glomerular lesion in one glomerulus (C: PAM stain, ×800). On immunohistochemistry, deposition of IgA (arrowheads in D) and C3 (arrowheads in E) was noted in a mesangial granular pattern (D: IgA stain; E: C3 stain; D, E: ×600). On electron microscopy, small electron-dense deposits (arrowheads in F) were evident in paramesangial areas (×5,000).

obsolescent, with slight segmental mesangial proliferative le-
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glucomerulitis. As shown in the figure, both the rash (Fig. 1b) and arthralgia nearly disappeared soon after the treatment

creatinine level increased to 1.93 mg/dL. Additionally, ster-
roid pulse therapy was administered one week after tonsil-
tomy. As follow-up treatment, prednisolone at a dose of 30 mg/day was administered for one month, after which the dose was reduced to 30 mg every other day. Simultaneously, MZR was started at a dose of 150 mg/day. Unfortunately, the patient developed diabetes developed after receiving the steroid pulse therapy, and it was necessary to prescribe a dipeptidyl peptidase-4 inhibitor until the steroid dose could be reduced. Meanwhile, the rash and arthralgia improved, but did not disappear, immediately after tonsillectomy, while the serum IgA level, which decreased after the procedure, gradually increased again. Taking into consideration the ex-
istence of other focal infections, we started treatment [appli-
cation of 1% zinc chloride and Japanese apricot extract (MK 615) nose drops] for the upper pharynx 10 months after ton-
sillectomy. As shown in the figure, both the rash (Fig. 1b) and arthralgia nearly disappeared soon after the treatment

Bilateral tonsillectomy was performed one month after the renal biopsy. Although treatment with NSAIDs and cy-
closporine was halted after the biopsy, the patient’s serum
for chronic epipharyngitis. There was no need for antiphlogistic analgesics. The IgA level decreased again, and the hematuria completely disappeared. In addition, the doses of steroids and MZR were reduced without signs of worsening, and the patient’s proteinuria and renal function gradually improved. Twenty months after tonsillectomy, the serum creatinine level had decreased from 1.93 to 1.55 mg/dL (Fig. 3).

Discussion

Performing tonsillectomy combined with steroid pulse therapy for IgAN at an early stage is expected to keep urine abnormalities in remission (5). However, the therapeutic effect is unclear in cases in which a longer time has elapsed from the onset of symptoms and/or patients with a history of prior renal dysfunction. In the current case, the renal biopsy showed that nearly half of the glomeruli were obsolescent and the tubulointerstitial lesion had progressed. Therefore, the pathological diagnosis was IgAN with few active lesions, although the lesions were predominantly chronic. We previously reported that the use of steroid pulse therapy in combination with MZR following tonsillectomy is effective in improving urinary findings and preserving the renal function when treating IgA nephropathy in patients with renal impairment (6, 7).

It is recognized that the administration of MZR combined with 14-3-3 protein and HSP60 enhances the transcriptional activity of glucocorticoid receptors and thus the effect of steroids (8). It has also been reported that MZR inhibits the action of α3β1 integrin and decreases the motility of fibroblast-specific protein-1-positive fibroblasts, both of which are involved in the progression of interstitial fibrosis in patients with IgAN (9).

It was recently demonstrated that activated macrophages play an important role in the pathology of IgAN (10). Additionally, steroid-induced increases in transforming growth factor-β production by macrophages are reportedly suppressed by the concomitant use of MZR. MZR not only potentiates steroidal anti-inflammatory effects, but also prevents the progression of chronic lesions, such as those involving tissue fibrosis and sclerosis, by inhibiting activated macrophages.

Steroid therapy is usually terminated within six months to one year. However, in this case, we continued treatment with low-dose steroids due to the patient’s joint pain. Consequently, the serum creatinine level temporarily worsened after starting this therapy. We consider two possible causes underlying this phenomenon: (a) the high dose of steroids temporarily deteriorated the patient’s renal function and induced glucose tolerance, and (b) the treatment of one course of steroid pulse therapy combined with MZR takes longer to achieve an effect than three courses of steroid pulse therapy alone. In our experience, we have observed improvements in the renal function several months after beginning MZR treatment.

In this case, the patient’s rash caused by psoriatic arthritis and arthralgia significantly improved soon after starting the above therapy. Psoriatic arthritis is a form of chronic inflammatory arthritis accompanying psoriasis of the skin. This disease is diverse, and, in some patients, progressive joint lesions cause functional disturbances. The appearance of a rash may significantly decrease the quality of life (QOL) of the patient from both mental and physical perspectives to the same degree as malignant tumors (11). It has been reported that T cells, especially Th1 cells, play a central role
in the clinical onset of psoriasis. For example, a recent report indicated that Th1 cells, Th17 cells and regulatory T cells (Treg) are mutually and intricately associated with chronic clinical states (12). It is therefore expected that inhibition of TNF-α, an inflammatory cytokine, reduces inflammation, suppresses epidermal growth and normalizes abnormal cornification. Effects on articular symptoms are also expected, and joint breakdown may be inhibited. TNF-α inhibitors, such as infliximab and adalimumab, are increasingly used in refractory cases. However, the burden of these drugs is high, and it has been reported that serious side effects occur at approximately twice the rate in patients older than 65 years of age than in those younger than 65 years of age (13).

Tonsillectomy has been shown to be very effective for palmoplantar pustulosis, sternocostoclavicular hyperostosis and IgAN. It has also been documented that these diseases coexist with one another at a high rate. Many reports have indicated that tonsillectomy has far-reaching effects on psoriasis, rheumatoid arthritis and Behçet’s disease in addition to the diseases listed above. Nyfors et al. described 74 cases of psoriasis vulgaris treated with tonsillectomy, reporting improvements in the rashes in 53 cases (72%) (2).

It has been speculated that an abnormal immune response in the tonsils causes and/or worsens the diseases described above. For example, Takahara reported that, on quantitative immunohistological analyses of tonsillar tissues, the overall area of T cell nodules is significantly expanded, whereas that of B-lymphoid follicles is reduced, and the number of apoptotic cells is elevated in tonsils obtained from patients with psoriasis and palmoplantar pustulosis than in those with recurrent tonsillitis. The area of T cell nodules and number of apoptotic cells are significantly larger in the tonsils of patients exhibiting a complete recovery after tonsillectomy than in those without a complete recovery (14).

In the present case, the rash initially improved after tonsillectomy and was further ameliorated after starting treatment for chronic epipharyngitis. It was recently reported that laryngological sources of infection are found in 44% of patients with psoriatic arthritis (15). Moreover, the effectiveness of cholecystectomy in removing the inflammatory focus as a treatment for psoriasis has also been reported (16). These facts suggest the presence of various factors in the pathogenesis of psoriasis and the contribution of multiple inflammatory foci in addition to the tonsils.

The mucosal surface of the upper pharynx forces back pathogenic microbes, such as bacteria and viruses, that are continuously intruding, while possessing mechanisms which allow it to coexist with resident microbiota. Secretory IgA performs a crucial function in this system. The lumen surface of the upper pharynx is covered with lymphocytes in a state of activation, and class II antigen-positive ciliated epithelial cells with an antigen-presenting ability are present in the tonsillar crypt epidermis. It has also been reported that the phenotype of lymphocytes obtained by scratching the epipharynx closely resembles that of lymphocytes in the palatine tonsils (17). Chronic epipharyngitis may be a cause of focal infection related to the development of secondary diseases.

The present patient was diagnosed with coexisting chronic epipharyngitis, as the application of a winding cotton swab containing 1% zinc chloride solution caused bleeding and scratching pain. We directly applied zinc chloride, which causes tissue convergence and corrosion and possesses an antibacterial activity, in addition to nose drops comprising MK615 to treat the patient’s chronic epipharyngitis. MK615 is a compound made by condensing and extracting Japanese apricot and has been reported to have various effects, including antitumor, anti-inflammatory and liver-supporting functions. MK615 inhibits the release of cytokines, such as TNF-α and IL-6, and may represent a useful therapeutic agent for chronic periodontitis, a condition that is also reported to cause focal infections (18, 19). In our facility, we have used nose drops containing MK615 for chronic epipharyngitis for several years. The curative effect is high, based on our experience, with no concerns regarding safety. Nevertheless, further studies are required to investigate the effects of local MK615 application as an adjunctive treatment.

Bleeding and pain resulting from the application of zinc chloride to the epipharynx was reduced via successive applications in this case. At the same time, the patient’s rash and arthralgia were further alleviated and the hematuria completely disappeared. However, it is necessary to accumulate further cases involving this treatment in order to confirm whether these agents are effective in cases of chronic epipharyngitis.

In summary, we experienced a case of IgAN with coexisting psoriatic arthritis in which we administered steroids and MZR in addition to treatment for focal infection. Consequently, the patient’s rash, arthralgia and renal function improved and the hematuria completely disappeared. Although this is a single case report, our findings indicate that combination treatment for focal infection, including steroids and MZR, is effective for multiple pathological conditions that may share a common source.

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

References
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