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Successful Treatment of Adult IgA Nephropathy with Nephrotic-Level Proteinuria by Combination Therapy Including Long-Term Coadministration of Mizoribine

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Key Words
IgA nephropathy · Mizoribine · Corticosteroid · Tonsillectomy

Abstract
A 41-year-old male patient was admitted to our hospital due to massive proteinuria and hematuria. His 24-hour urinary protein excretion and the number of urinary erythrocytes were 3.91 g/day and 50–99/high-power field, respectively. A renal biopsy showed a severe pathological pattern of immunoglobulin A nephropathy (IgAN) that involved marked endocapillary proliferation and segmental sclerosis (Oxford-MEST score: M0, E1, S1, T0). Because he had nephrotic-level proteinuria with severe pathological findings, which are tonsillectomy and corticosteroid pulse therapy-resistant characteristics, he received mizoribine for a long period as part of the combination therapy using corticosteroid, tonsillectomy, dipyridamole, warfarin and renin-angiotensin-aldosterone system blockers. Twelve months after the beginning of treatment, his urinary findings were normal. In this report, we describe the pathological findings and successful treatment course, and discuss the potential effects of long-term coadministration of mizoribine for adult IgAN treatment.

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Introduction

Immunoglobulin A nephropathy (IgAN) is the most common glomerulonephritis, and the long-term prognosis of IgAN is variable because of the diversity of disease activity and long-term treatments among patients. Many therapeutic regimens for IgAN have been reported [1], however, some patients still respond poorly to these regimens, especially in severe or advanced IgAN. Patients who had massive proteinuria at the time of renal biopsy had a poor renal prognosis even if they received currently accepted intensive therapy [2]. Therefore, improved treatment regimens are required for those with therapy-resistant characteristics. In this report, we describe the renal pathological findings using the Oxford-MEST score [3] and the successful treatment course of an adult IgAN patient with nephrotic-level proteinuria at the time of diagnosis, and we discuss the potential effects of long-term coadministration of mizoribine (MZR) for adult IgAN treatment.

Case Report

A 41-year-old male patient was diagnosed with proteinuria and hematuria by medical examination in June 2009, and he consulted us in November 2009 without receiving any treatment. Laboratory testing revealed blood pressure (BP) 142/80 mm Hg, 24-hour urinary protein excretion (UPE) 3.91 g/day, number of urinary erythrocytes (uRBC) 50–99/high-power field (HPF), granular cast (+), serum creatinine 0.72 mg/dl, estimated glomerular filtration rate 96 ml/min/1.73 m^2, and serum IgA 162 mg/dl. His renal biopsy specimen contained 48 glomeruli. The percentages of glomeruli showing global sclerosis, mesangial hypercellularity, segmental glomerulosclerosis, endocapillary hypercellularity, and crescents were 4.2, 41.7, 4.2, 16.7, and 12.5% (fibrocellular crescents 6.3%, fibrous crescents 6.3%), respectively. The percentage of interstitial fibrosis/tubular atrophy of the cortical area was 20%. Immunohistochemistry showed coarse granular deposits of IgA and C3 predominantly in the mesangium. Based on these clinicopathological findings, a diagnosis of primary IgA nephropathy was made. In accordance with the Oxford-MEST score [3], his pathological findings were classified as M0, E1, S1, T0. In addition, numerous CD68-positive macrophages were observed in both glomeruli and interstitium (**fig. 1**).

After diagnosis of IgAN, treatment with olmesartan 20 mg/day, dipyridamole 150 mg/day, and warfarin 1 mg/day was begun (**fig. 2**). Because he had nephrotic-level proteinuria, we could not perform tonsillectomy before corticosteroid therapy. Therefore, MZR 150 mg after each breakfast and corticosteroid therapy (500 mg methylprednisolone for three consecutive days in months 1, 3, and 5, and 0.5 mg/kg prednisolone every other day) were initiated 2 weeks later. The oral prednisolone dosage was reduced during the next month. Under this regimen, the serum concentration of MZR 3 h after administration [4] was 0.85 μg/ml. As his BP did not fall below 130/80 mm Hg, amlodipine 5 mg/day was administered. However, it was discontinued because of liver damage. After corticosteroid therapy, UPE and uRBC had decreased to 0.62 g/day and 5–9/HPF, respectively, and the risk that he might contract the infectious disease decreased. He then underwent a tonsillectomy. Thereafter, olmesartan was increased from 20 to 40 mg/day, and his BP was 130/68 mm Hg in October. As proteinuria remained, eplerenone (25 mg/day) was administered. Urinary findings normalized 12 months after the beginning of treatment (UPE 0.17 g/day and uRBC 1–4/HPF). Six months later, MZR was discontinued. Neither proteinuria nor hematuria had recurred at the time of writing this paper.

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Discussion

At present, angiotensin II (AngII) inhibition and corticosteroid therapy are generally used for IgAN treatment [1]. To improve efficacy, a combination of 'tonsillectomy and corticosteroid pulse' (TSP) therapy has been proposed. Nationwide survey of TSP therapy for IgAN in Japan reported a high rate of complete remission with TSP therapy, almost 50% [5]. Unfortunately, our patient had massive proteinuria and severe pathological findings initially, which are TSP therapy-resistant characteristics [5]. Therefore, an improved treatment regimen was required.

Recently, the use of immunosuppressants for IgAN treatment has been discussed [1]. Adding low-dose azathioprine (AZA) to corticosteroids for 6 months does not benefit IgAN treatment [6]. In contrast, combination therapy including AZA for 2 years was effective against childhood proliferative IgAN [7]. Instead of AZA, MZR is frequently used for childhood IgAN because of its relative lack of toxicity [8]. The immunosuppressive effects of MZR have been shown to be due to the inhibition of DNA synthesis in the S phase of the cell cycle. Renoprotective effects of MZR, such as amelioration of tubulointerstitial fibrosis by inhibition of tubular osteopontin expression [9] and inhibition of renal macrophage accumulation resulting in prevention of glomerulosclerosis and interstitial fibrosis [10] have also been demonstrated. Clinically, MZR significantly reduced proteinuria and hematuria with histological improvement and caused fewer complications than the conventional immunosuppressants. Moreover, a cocktail therapy using prednisolone, MZR, warfarin, and dipyridamole decreased UPE, hematuria, and renal lesions in childhood IgAN [11]. The effects of this MZR combination therapy were similar to those of the AZA combination, and the side effects of the MZR combination were clearly milder than those of the AZA combination [7]. These reports suggest that long-term coadministration of MZR may improve the prognosis of adult IgAN. Only a few case reports have examined the efficacy of MZR in adult IgAN. Kaneko et al. [12] reported the effects of MZR and TSP combination therapy in IgAN patients with an average proteinuria being below 1 g/day. In their treatment regimen, the total dose of corticosteroids was reduced instead of administering MZR. Because our patient had nephrotic-level proteinuria with severe pathological findings, we decided to administer MZR for a long period as part of the combination therapy. As a result, he showed an excellent prognosis without any serious adverse effects.

For the reason of successful clinical course, the following mechanisms are further discussed. First, numerous CD68-positive macrophages were observed in both glomeruli and interstitium in this patient (fig. 1). MZR has been reported to attenuate renal injury and macrophage infiltration [9, 10, 13]. Kikuchi et al. [10] reported that both glomerulosclerosis and interstitial fibrosis were reduced by MZR via suppression of macrophage infiltration in non-insulin-dependent diabetic rat. Furthermore, Tanaka et al. [13] reported that intraglomerular macrophage infiltration and chronicity indices tended to decrease more in patients who received immunosuppressive treatment with MZR than in patients who received immunosuppressive treatment alone, in patients with severe lupus nephritis. Although, corticosteroid has strong immunosuppressive and anti-inflammatory effects, it is considered that long-term coadministration of MZR may have additive and beneficial therapeutic effects in this patient. Second, after administration of eplerenone, the amount of proteinuria reduced. This effect was

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consistent with a previous study which showed antiproteinuric effect of the addition of low-dose eplerenone (25–50 mg/day) to renin-angiotensin system blockers in nondiabetic chronic kidney disease patients [14]. Recent studies suggested that aldosterone exerts deleterious effects in the vascular system and kidney independently of angiotensin II [15]. Eplerenone reduced osteopontin and expression of proinflammatory molecules, with consequent attenuation of renal damage and inflammation [16]. In this patient, there was no remarkable fall in blood pressure after administration of low-dose eplerenone (fig. 2), suggesting effects of eplerenone might be mediated by BP-independent mechanisms [14–17]. A prospective cohort study will be required to clarify the characteristics of regimen-sensitive patients.

Disclosure Statement

There are no disclosures.

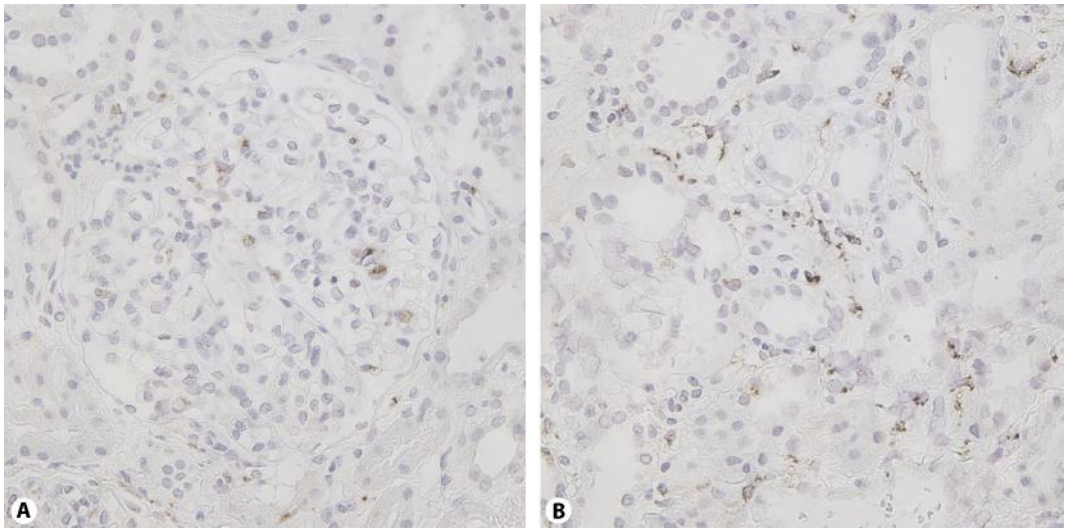

Fig. 1. Macrophage infiltration in glomeruli and interstitium. Representative micrographs of CD68 staining are shown. Note numerous CD68-positive macrophages in glomeruli (**A**) and interstitium (**B**). Original magnification: ×200.

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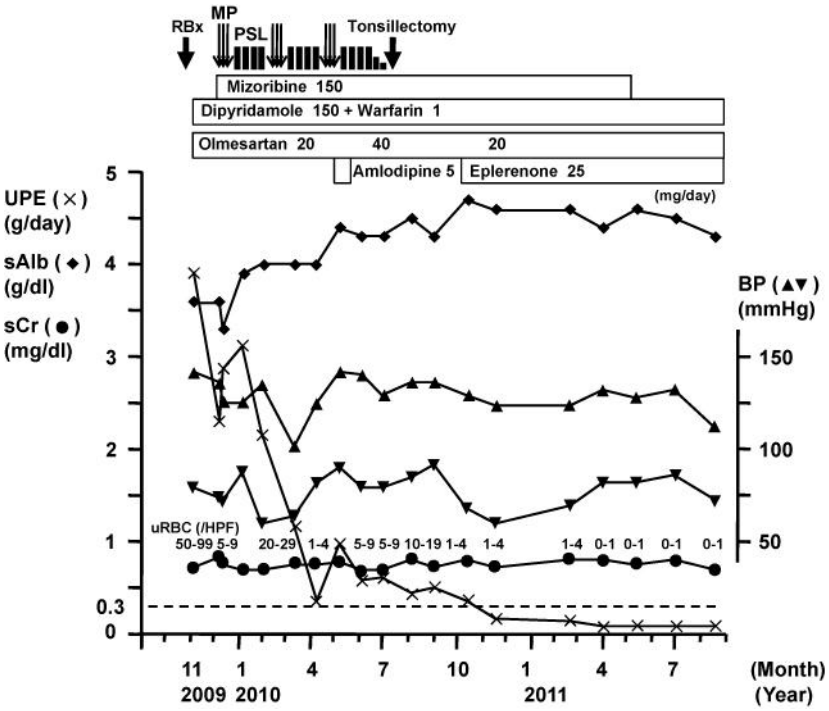

Fig. 2. The clinical course of a 41-year-old male patient with IgA nephropathy who received combination therapy including mizoribine. Longitudinal changes in 24-hour protein excretion (UPE), serum albumin (sAlb), serum creatinine (sCr), the number of urinary erythrocytes (/high-power field) (uRBC/HPF), and blood pressure (mm Hg) are shown. Note the apparent improvements in UPE and uRBC 12 months after beginning the combination therapy.

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