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*Case Report*

# IgA Nephropathy Complicated with X-linked Thrombocytopenia

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**Renal involvement is occasionally observed in Wiskott-Aldrich syndrome (WAS) and X-linked thrombocytopenia (XLT). It has been reported that galactose-deficient IgA is a closely linked to IgA nephropathy (IgAN), suggesting that patients with XLT/WAS associated with reduced galactosylation on serum IgA are susceptible to IgAN. It is necessary to pay more attention to patients with IgAN due to the potential complication with XLT/WAS. We here present a patient of XLT complicated with mild IgAN who underwent tonsillectomy combined with steroid pulse therapy to achieve complete clinical remission.**

**Key words:** IgAN nephropathy, Wiskott-Aldrich syndrome, X-linked thrombocytopenia, galactose-deficient IgA1

IgA nephropathy is the most common glomerulonephritis in Japan. Renal biopsy is essential to diagnose this disease. Upon diagnosis, patients with IgA nephropathy are immediately treated with an appropriate remission induction therapy to prevent chronic renal failure. Among the several ideal treatment strategies for IgA nephropathy, a tonsillectomy plus steroid pulse therapy has successfully achieved complete remission without any fatal or other adverse effects [1-3].

Wiskott-Aldrich syndrome (WAS) is defined as an inherited blood cell disorder due to mutations in the X-chromosome gene WASP (Wiskott-Aldrich syndrome protein), which was characterized originally by thrombocytopenia, immunodeficiency and eczema [4]. WASP consists of 12 exons containing 1823 base pairs. It encodes a 502-amino acid protein that is expressed selectively in hematopoietic stem cell-derived lineages [5-8]. WASP gene mutations result in three distinct clinical phenotypes: classic WAS, X-linked thrombocytopenia (XLT), and X-linked neutropenia (XLN) [9,10]. Mutations that completely avert WASP expression typically lead to the classic phenotype. Missense mutations resulting in the expression of defective WASP, often in a reduced quantity of mature protein, most often result in the XLT phenotype, sometimes with only intermittent thrombocytopenia [11]. XLN is caused by gain-of-function mutations that result in constitutively activated WASP [12-14].

Renal involvement has been occasionally observed in WAS and XLT [15,16]. So far, the pathogenesis of WAS/XLT-associated nephropathy remains unclear, because the tendency of patients with WAS/XLT-associated nephropathy to bleed renders renal histopathology difficult. Here we describe a case of a patient with XLT who was diagnosed with IgA nephropathy (IgAN) by renal biopsy and then successfully treated

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with tonsillectomy combined with steroid pulse therapy.

## Case Presentation

The patient was a 16-year-old man. At the age of 3 months, he developed systemic and oral purpura and was referred at that time to a hospital, where laboratory data revealed that he had thrombocytopenia (26,000/mm$^3$), but no abnormality was observed in a bone marrow biopsy. Further, he had neither anti-platelet antibody nor virus infection. Given these observations, he was suspected of having Wiskott–Aldrich syndrome (WAS). A genetic investigation demonstrated that he had a WASP gene mutation (details of the mutation are unavailable). However, he did not show any immune disorder. Finally, he was diagnosed with X-linked thrombocytopenia (XLT), a mild case of WAS. After that, he showed no symptoms and his doctor took a wait-and-see approach on an outpatient basis. His platelet count was kept to about 70,000~90,000/mm$^3$.

Fifteen years later, he presented with hematuria at a routine school health check. Further, he developed proteinuria (0.45 g/gCr) a year after that, and then was referred to our hospital for a renal biopsy.

He had anamnestic history of macrohematuria after tonsillitis but no skin purpura and no arthritic pain. His familial history was as follows. His paternal aunt had end-stage renal disease and was on dialysis. His paternal grandfather had died of lung cancer. His maternal uncle had died of esophageal cancer. He did had no leg edema, skin purpura, or tonsil enlargement according to a physical examination. His body temperature was 36.5 °C and his blood pressure was 102/66 mmHg. His consciousness was clear and he had no symptoms suggestive of neurological, respiratory, or abdominal involvement. Laboratory findings are summarized in Table 1. The serum levels of Cr, IgA, IgG, IgM, complement (C) 3 and C4, and total hemolytic complement (CH50) were within the normal ranges. Urinalysis showed that he did not have proteinuria (qualitative test negative, 0.09 g/gCr) but did have hematuria (sediment containing 103.4 red blood cells (RBCs) per high power field). Computed tomography (CT) showed no abnormalities in the urogenital tracts. Thus, we made a possible clinical diagnosis of chronic glomerulonephritis. To obtain a histopathological diagnosis, we performed percutaneous renal biopsy. The histological findings were as follows. Light microscopy identified a slight tubulointerstitial disorder (atrophied and fibrotic area was <5% of the whole area) and 29 glomeruli with 1 small fibro-cellular crescent (Fig. 1A and B) and 1 adhe-

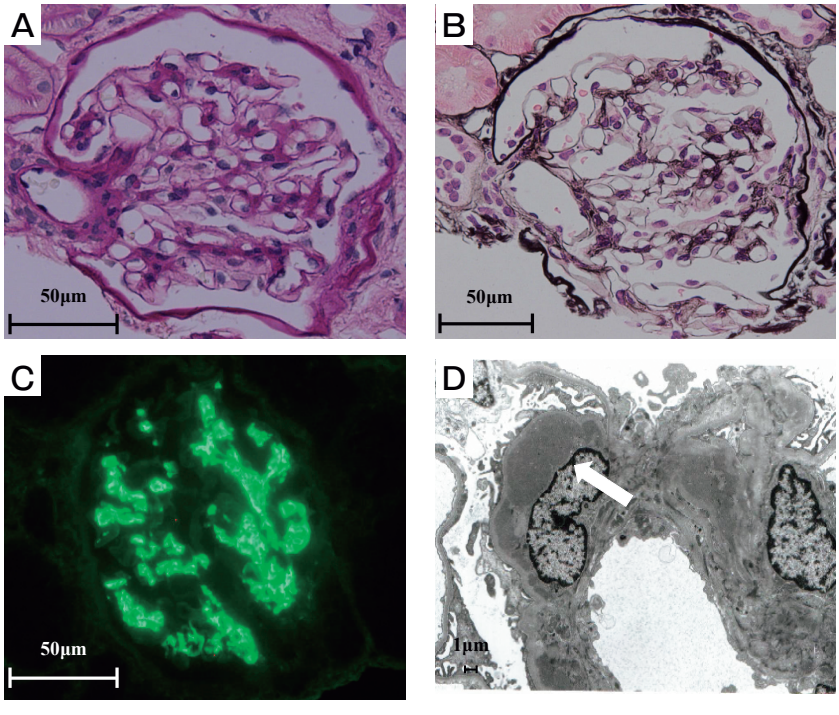


**Fig. 1** Findings of renal biopsy. (**A** and **B**) Light microscopy showing a small fibrocellular crescent in PAS stain (**A**) and in PAM stain (**B**). (**C**) Immunofluorescence showing a strong and granular deposition of IgA (3+) in the mesangial area. (**D**) Electron microscopy exhibiting numerous electron-dense deposits in the mesangium. White asterisk denotes a large hemispherical deposit characteristic of IgA nephropathy. PAS, Periodic acid—Schiff; PAM, Periodic acid—methenamine—silver; Ig, immunoglobulin.

Table 1 Laboratory data

| | | | | | |
|---|---|---|---|---|---|
| Peripheral blood | | Serological test | | Coagulation−fibrinolysis system | |
| WBC (/μl) | 4370 | CRP (mg/dl) | 0.07 | PT (second) | 11.5 |
| RBC ($\times 10^4$/μl) | 464 | CH50 (U/ml) | 45 | PT (%) | 98 |
| Hb (g/dl) | 13.6 | C3 (mg/dl) | 90.0 | PT-INR | 1.01 |
| Plt ($\times 10^4$/μl) | 12.7 | C4 (mg/dl) | 25.2 | APTT (second) | 30.0 |
| MPV (fl) | 8.5 | IgG (mg/dl) | 1154.9 | Fibrinogen (mg/dl) | 30.4 |
| Blood chemistry | | IgA (mg/dl) | 260.6 | FDP (μg/ml) | 3.0 |
| TP (g/dl) | 6.8 | IgM (mg/dl) | 28.5 | D-dimer (μg/ml) | 0.9 |
| Alb (g/dl) | 4.2 | IgA/C3 ratio | 2.90 | Urinalysis | |
| AST (IU/l) | 15 | Rheumatoid factor (IU/ml) | 1.5 | pH | 7.5 |
| ALT (IU/l) | 10 | ANA | 0.12 | Urine protein | (±) |
| LDH (IU/l) | 150 | PR3-ANCA (IU/ml) | <0.50 | UTP/Cr (g/gCr) | 0.09 |
| BUN (mg/dl) | 9.4 | MPO-ANCA (IU/ml) | <0.50 | Occult blood | (2+) |
| Cr (mg/dl) | 0.73 | Anti-GBM antibody (U/ml) | <1.40 | Sediment RBC (/HPF) | 103.4 |
| UA (mg/dl) | 4.5 | Tumor marker | | Sediment WBC (/HPF) | 0.3 |
| Na (mmol/l) | 140 | CEA (ng/ml) | 0.42 | U-NAG (U/L) | 6.0 |
| K (mmol/l) | 3.8 | CA19-9 (U/ml) | 3.8 | U-$\beta_2$MG (mg/l) | 0.20 |
| Cl (mmol/l) | 105 | Serum immunoelectrophoresis | | Urine immunoelectrophoresis | |
| Ca (mmol/l) | 8.9 | Monoclonal protein | (−) | BJP | (−) |
| P (mmol/l) | 3.1 | | | Monoclonal protein | (−) |

WBC, white blood cell value; RBC, red blood cell; Hb, hemoglobin value; Plt, platelet value; MPV, mean platelet volume; TP, serum total protein value; Alb, serum albumin value; AST, serum aspartate aminotransferase value; ALT, serum aspartate aminotransferase value; γGTP, serum γ-glutamyltransferase value; LDH, serum lactate dehydrogenase value; BUN, blood urea nitrogen level; Cr, serum creatinine level; UA, serum ureic acid concentration; Na, serum sodium concentration; K, serum potassium concentration; CL, serum chloride concentration; Ca, serum calcium concentration; P, serum phosphate concentration; CRP, serum C-reactive protein level; CH50, serum total hemolytic complement level; C3, serum complement C3 level; C4, serum complement C4 level; IgG, serum immunoglobulin G level; IgA, serum immunoglobulin level; IgM, serum immunoglobulin M level; ANA, serum antinuclear antibody level; PR3-ANCA, proteinase-3-antineutrophil cytoplasmic antibody; MPO-ANCA, myeloperoxidase-antineutrophil cytoplasmic antibody; GBM, glomerular basement membrane; CEA, serum carcinoembryonic antigen level; CA19-9, serum carbohydrate antigen 19-9l evel; PT, prothrombin time; PT−INR, prothrombin time − international normalized ratio; APTT, activated partial thromboplastin time; FDP, fibrin degradation products; HPF, high-power field; UTP/Cr, urine total protein to creatinine ratio; U-NAG, urine N-acetyl-β-D-glucosaminidase level; U-$\beta_2$MG, urine $\beta_2$ microglobulin level; BJP, Bence Jones proteinuria.

sion. Immunofluorescent examination revealed a strong IgA granular deposition (3+) in the mesangial area (Fig. 1C), along with mesangial staining for IgG (1+) and C3 (1+). Furthermore, electron microscopy demonstrated numerous electron-dense deposits in the mesangial area (Fig. 1D). On the basis of these findings, the diagnosis of IgA nephropathy was confirmed. Therefore, we performed tonsillectomy and steroid pulse therapy to achieve complete clinical remission. He underwent tonsillectomy 7 months after the diagnosis. Four months after the tonsillectomy, he received steroid pulse therapy (high-dose methylprednisolone (0.5 g/day for 3 days for three courses) followed by oral prednisolone at an initial dose of 30 mg/day on alternate days). Sixteen days after the steroid pulse therapy, he had no hematuria. After being discharged from our hospital, he received oral prednisolone treatment with a gradual decrease in dosage over 1 year at his local doctor's office. He is on a good course. From the viewpoint of therapeutic diagnosis, we considered that he actually developed IgAN, and that tonsillectomy and steroid pulse therapy were well tolerated without any major adverse events.

## Discussion

We experienced a case of XLT who was diagnosed with IgAN by renal biopsy. The patient received tonsil-

lectomy plus steroid pulse therapy and has maintained remission after the treatment.

His histological abnormality obtained by renal biopsy was mild. However, an occasionally reported complication associated with XLT is IgA nephropathy leading to chronic renal failure. Actually, he had anamnestic history of macrohematuria after tonsillitis. In consideration of his youth, he should have a very long time to live. If his tonsillitis relapses repeatedly, it could aggravate the symptoms of IgAN for the rest of his life. Kawaguchi *et al.* [17] reported that steroid pulse therapy combined with tonsillectomy significantly increased the probability of clinical remission, which was defined as negative proteinuria by dipstick testing and urinary erythrocytes of less than 1/high-power field in IgAN patients with glomerular hematuria and minimal proteinuria; those authors found that this combination of therapies was more effective in patients with less-severe histological findings. Our patient showed marked hematuria (sediment RBC 103.4/HPF). We anticipated that steroid pulse therapy combined with tonsillectomy could allow our patient to achieve that definition of clinical remission, and indeed this approach resulted in complete clinical remission.

IgAN is recognized as the most common glomerular disease in Asia and some countries in Europe [18-20]. The clinical manifestations vary; microscopic hematuria and proteinuria are the most common ones. However, approximately 15% to 20% of affected patients progress to end-stage renal disease (ESRD) within 10 years, and 40% within 20 years [21]. There are several therapeutic options, such as immunosuppressive treatment and blood pressure control with a renin–angiotensin system [22]. In Japan, tonsillectomy combined with steroid pulse therapy has been demonstrated to have a good clinical outcome in patients with IgAN [23]. Currently histopathological analysis of renal biopsies is considered the gold standard for diagnosis and contributes to both the making of therapeutic strategy and the prediction of prognosis [24]. The histopathological hallmark of IgAN is the predominance of deposition with immune complex containing IgA in mesangial regions, but its pathogenetic factors remain obscure. Previous studies have revealed that aberrantly glycosylated IgA1 plays an important role in the pathogenesis of IgAN [25-28], *e.g.*, the hinge-region O-linked glycans are galactose-deficient [29]. Yasutake *et al.* [30] reported that the serum level of galactose-deficient IgA1 (Gd-IgA1) tended to be higher in IgAN patients than in patients with other renal or nonrenal diseases. We have measured the serum levels of Gd-IgA1 in patients with IgAN, which ranged from 1.5 to 21.4 μg/mL (n = 20, average value, 5.9 ± 4.9 μg/mL), and found the results comparable to those reported. In the present case, no marked increase in the serum level of Gd-IgA1 was seen (3.2 μg/mL).

XLT is a congenital disorder characterized in general by thrombocytopenia and small platelets, without any other complications of WAS. The pathogenesis is a mild allelic variant caused by mutations in the WASP gene [31]. Since patients with XLT rarely have serious immune disorders compared with WAS patients, they tend to have better prognoses than WAS patients. Actually, XLT patients show excellent long-term survival compared to WAS patients [32]. On the other hand, XLT patients do not always experience event-free survival [32]. The occasionally reported complications associated with XLT are severe bleeding, cancer, and IgA nephropathy leading to chronic renal failure [31]. There are several case reports of WAS/XLT associated with nephropathy, but few patients receive a renal biopsy due to the bleeding tendency in WAS/XLT (Table 2) [15, 33-42]. More patients with WAS/XLT are male than female, but this might be because WAS/XLT occurs more often in men. Our patient was close to the mean age for the onset of nephropathy in WAS/XLT, as seen in Table 2. Therefore, we consider that our patient developed IgA nephropathy associated with XLT.

In their experimental model, Shimizu *et al.* [43] revealed that serum IgA and IgA production by splenic B cells increased in WASp-deficient mice compared to wild-type mice. The levels of sialylation and galactosylation of N-glycans in serum IgA in Was-KO mice were significantly reduced. This indicated that the production of aberrant IgA production increased in WASp-deficient mice. In a clinical setting, Hoshino *et al.* [40] reported that IgAN patients with XLT were clinically and histologically improved after bone marrow transplantation (BMT), indicating that the increased IgA production and aberrant glycosylation of IgA may be critically involved in the pathogenesis of glomerulonephritis in WAS/XLT. At present, several hypotheses have been proposed to explain the relationship between IgA nephropathy and WAS/XLT. As described previously [43], the production of aberrant IgA increases in

Table 2 Clinical and pathologic findings of nephropathy associated with WAS/XLT

| Patient No. | Age | Gender | Clinical diagnosis | Serum IgA level (mg/dl) | Pathologic findings | Reference No. |
|---|---|---|---|---|---|---|
| 1 | 2 | Male | WAS | Not described | Interstitial nephritis | 15 |
| 2 | 4 | Male | WAS | Not described | Chronic proliferative GN with focal crescent formation | 15 |
| 3 | 12 | Female | WAS variant | Elevated | Immune-complex GN IF: IgA and IgM, C3 | 33 |
| 4 | 46 | Male | WAS | Elevated | MPGN with crescent and mesangial IgA deposit | 34 |
| 5 | 33 | Male | WAS | Elevated | MPGN IF: negative for IgA | 35 |
| 6 | 12 | Male | WAS | Elevated | MPGN IF: IgA | 36 |
| 7 | 35 | Female | WAS carrier | Normal | Diffuse proliferative GN with cellular crescent IF: IgA, fibrinogen, C3 | 37 |
| 8 | 8 | Male | XLT | Elevated | IgAN IF: IgA, C3 | 38 |
| 9 | 35 | Male | XLT | Normal | IgAN IF: IgA, C3 | 38 |
| 10 | 8 | Male | WAS | Elevated | IgAN with FSGS and focal ATIN IF: IgA, C3 | 39 |
| 11 | 8 | Male | XLT | Normal | IgAN IF: IgA, IgG | 40 |
| 12 | 21 | Male | WAS | Elevated | IgAN | 41 |
| 13 | 8 | Male | XLT | Not described | IgAN | 42 |
| 14 | 16 | Male | XLT | Normal | IgAN IF: IgA, C3 | Present case |

WAS, Wiskott–Aldrich syndrome; XLT, x-linked thrombocytopenia; IgAN, IgA nephropathy; C3, complement3; GN, glomerulonephritis; IF, immunofluorescence; MPGN, membranoproliferative glomerulonephritis; FSGS, focal segmental glomerular sclerosis; ATIN, acute tubulointerstitial nephriti.

WAS/XLT; that is, the immunodeficiency due to aberrant CD43 also increases susceptibility to infection, leading to increased IgA production [44]. Furthermore, because a deficient reticuloendothelial system cannot adequately remove IgA, IgA nephropathy is easily induced by recurrent infections and the infection-related formation of IgA immune complexes [36]. Because the aforementioned mechanisms are related to each other, patients with WAS/XLT might often develop IgA nephropathy. However, serum levels of Gd-IgA1 were not markedly increased in our patient. In addition, his histological abnormality obtained by renal biopsy was mild and the clinical symptom of IgAN was minor. Berthoux *et al.* [45] reported that the serum levels of IgA and Gd-IgA1 were positively associated with the progression of IgAN. Furthermore, the phenotypic level of XLT in our patient was not so severe. Actually, he had low-grade thrombocytopenia and no small platelets. In fact, certain proportions of patients with IgAN have non-increased serum levels of both IgA and Gd-IgA1. Further studies are required to investigate the serum levels of IgA and Gd-IgA1 as accurate surrogate markers of IgAN.

This is the first case of XLT complicated with mild IgAN that was treated with tonsillectomy combined with steroid pulse therapy. The treatment resulted in a good renal prognosis. Biopsy-proven kidney diseases, mainly IgAN, associated with WAS reportedly have very poor outcomes. Therefore, such patients have received aggressive treatments including kidney transplantation, splenectomy, and BMT. On the other hand, there are few reported cases of IgAN complicated with XLT, and the treatment has been inconsistent. Matsukura [38] reported 2 patients with IgAN associated with XLT. One of those patients was treated with low-dose oral prednisolone and angiotensin-converting enzyme inhibitor, but achieved only partial remission- The other patient developed ESRD requiring hemodialysis. Tonsillectomy combined with subsequent steroid pulse therapy may be a therapeutic strategy for mild IgAN with XLT. To evaluate its long-term prognosis, we will need a longer observation period and a larger number of patients.

In conclusion, we report a case of IgAN complicated with XLT that was successfully treated with tonsillectomy and steroid pulse therapy. This combined therapy may be worth considering in patients with a mild form of IgAN with XLT. We should be careful when dealing with patients with WAS/XLT, because they may develop IgA nephropathy, which this therapy

can treat.

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