

Wiskott-Aldrich syndrome with IgA nephropathy: a case report and literature review

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Abstract

The pathogenesis of renal involvement in Wiskott-Aldrich syndrome (WAS) is unclear and renal outcome is generally poor in such situations. Therefore, we present the case of an 8-year-old boy with WAS who developed hematuria, proteinuria, and declining renal function that did not improve with the combined use of immunosuppressive agents and angiotensin-converting-enzyme inhibitor. Renal pathology revealed IgA nephropathy (IgAN). He underwent splenectomy for refractory thrombocytopenia. The proteinuria remitted and renal function improved after splenectomy, long-term antibiotic prophylaxis and tapering of immunosuppressive agents.

Keywords: antibiotic prophylaxis; IgA nephropathy; splenectomy; Wiskott-Aldrich syndrome.

Abbreviations: Wiskott-Aldrich syndrome (WAS); IgA nephropathy (IgAN); X-linked thrombocytopenia (XLT); WAS protein (*WASP*); membranoproliferative glomerulonephritis (MPGN); end-stage renal disease (ESRD).

Introduction

Wiskott-Aldrich syndrome (WAS) is a rare X-linked disorder, caused by WAS gene mutation, characterized by the triad of profound thrombocytopenia with small platelets, eczema, and recurrent pyogenic and opportunistic infection[1]. X-linked thrombocytopenia (XLT) is a mild form of WAS. WAS gene maps to the region Xp11.22-p11.23 and is comprised of 12 exons in a 9-kb region [2]. The gene encodes a 502-amino acid intracellular protein, WAS protein (*WASP*), which is a key regulator of actin polymerization and facilitates the nuclear translocation of nuclear factor κ B in hematopoietic cells [2]. *WASP* also plays an important role in lymphoid development and in the maturation and function of myeloid monocytic cells [2].

Renal involvement in WAS has been rarely reported and it has been generally associated with poor renal outcome [3,4,6-7]. Renal histopathology is not easily available due to the bleeding tendency in WAS. The pathogenesis of renal involvement in WAS remains unclear. We report a case of WAS that developed IgA nephropathy with presentations of hematuria, proteinuria and declining renal function. The patient underwent splenectomy for refractory thrombocytopenia. The proteinuria remitted and renal function improved after splenectomy, long-term antibiotic prophylaxis and tapering of immunosuppressive agents.

Case report

An 8-year-old boy was referred to our hospital because of frequent pneumonia, otitis media, bloody diarrhea, and profound thrombocytopenia noted since 1 year of age. The thrombocytopenia was refractory to frequent platelet transfusion. There was no consanguinity between the patient's parents. The patient's uncle had suffered from thrombocytopenia since childhood. Physical examination showed multiple petechiae with ecchymosis and eczema over his extremities. Laboratory investigation revealed the following levels: hemoglobin, 5.1 g/dL; leukocytes, 4,690 cells/mm³; and platelets, 11,000 cells/mm³. Peripheral blood smear showed small platelets. Urinalysis revealed microscopic hematuria and proteinuria (>300 mg/dL). Blood creatinine level was 1.49 mg/dL. Bone marrow aspirate showed increased megakaryocytes without blast cells. Immunologic evaluation showed an IgM level of 36.8 mg/dL, IgA 687 mg/dL, IgG 1070 mg/dL, CH50 34 U/mL, C3 105 mg/dL, and C4 35 mg/dL. Antinuclear antibodies, anti-dsDNA antibodies, rheumatoid factor, and hepatitis B and C were negative.

WAS was diagnosed based on the clinical presentations. *WASP* mutation analysis was performed; insertion mutation at the 1023rd base pair in exon 10 and amino acid substitution (Leu342Thr) with a frame shift from 342 to the stop codon at 494 base pairs was found. The patient's maternal uncle was found to have an identical mutation. The patient's mother was found to be a carrier.

During hospitalization, the patient experienced *Citrobacter freundii* septicemia which was under control with prompt antibiotics treatment. However, declining renal function and heavy proteinuria progressed. He was administered Enalapril 2.5 mg/day and immunosuppressive agents (prednisolone, 40 mg/day; mycophenolate mofetil, 500 mg/day). However, renal function and proteinuria worsened. The patient

underwent a splenectomy for refractory thrombocytopenia and open renal biopsy. The kidney tissue specimen contained 28 glomeruli, 4 of which were completely obsolescent. The remaining glomeruli showed diffuse mesangial hypercellularity, with adhesion to Bowman's capsule. The interstitium showed inflammatory infiltrates, patchy tubular atrophy (up to 15%), and focal interstitial fibrosis. Immunofluorescent analysis indicated granular mesangial depositions of IgA and C3. IgAN was diagnosed (Fig. 1).

Post-splenectomy care followed the related guidelines, including life-long antibiotic prophylaxis and recommended immunization. The patient received trimethoprim-sulfamethoxazole, with the tapering off of immunosuppressive agents. Enalapril had been used for 6 months until proteinuria was ≤ 0.5 g/d. Renal function improved gradually and proteinuria was in remission, except for isolated microscopic hematuria, noted during over two years of follow-up (Fig. 2).

Discussion

The pathogenesis of WAS-associated nephropathy remains unclear, because such nephropathy is under-recognized and the pathology is not easily obtainable. Our patient is one of only a few in whom a complete clinical and molecular diagnosis was made, with early recognition resulting in a favorable outcome.

Renal involvement was thought to be uncommon in WAS, before Spitler et al. described its occurrence in 6 of 32 patients [4]. Standen observed nephropathy in 4 of 13 males with XLT, thought to be a variant of WAS [1]. Nevertheless, renal histological studies are limited because of the difficulty in performing renal biopsies due to the risk of hemorrhage. Literature-reported cases of WAS/XLT with biopsy proven nephropathy, including our case, are summarized in Table 1; only 3 (Case 8, 9, 10), including our case, had a genetic-based diagnosis. Renal pathology reports have shown various histological features, including membranoproliferative glomerulonephritis (MPGN), mesangial proliferative glomerulonephritis, interstitial nephritis, and IgAN [3-9]. Seven of 10 patients (70%) with nephropathy showed mesangial IgA deposition. In 8 patients, serum IgA level was assessed, with 6 showing elevated levels; the remaining 2 had normal serum IgA levels, but showed mesangial IgA deposition. Most WAS/XLT patients had an unfavorable renal outcome. Among 4 adult patients with end-stage renal disease (ESRD), 2 required long-term dialysis and 2 had to undergo renal transplantation. Among 2 patients who underwent splenectomy and long-term antibiotic prophylaxis, including our patient, both showed subsequent stable renal function.

Treatment of WAS-associated nephropathy remains controversial, with no proven curable or promising treatment available at this time. Webb et al. described 1 patient with WAS and MPGN who recovered after renal transplantation while being

able to avoid aggressive immunosuppressive regimes [8], illustrating the possible safety of renal transplantation in WAS patients. However, another patient with MPGN experienced cellular rejection after receiving renal transplantation [7]. Moreover, Fischer et al. reported a fatal case of renal transplantation in a patient with WAS-associated nephropathy, concluding that renal transplantation remains a high-risk procedure due to the possibility of rejection and the increased propensity for developing infection and lymphoma [10]. Unfortunately, renal replacement therapy seems to be a safer therapy in order to achieve long-term survival in WAS patients developing ESRD [3,6].

Hematopoietic stem cell (HSC) transplantation seems to be the curative therapeutic option for WAS. Transplant is, however, associated with the significant risk of morbidity and mortality and this should be taken into consideration. In patients with no available matched donor, treatment is mainly supportive with intravenous gammaglobulin, prophylactic antibiotics and immunization. Splenectomy effectively normalizes platelet counts and reduces serious bleeding. Antibiotic prophylaxis minimizes the risk of post-splenectomy sepsis, and changes splenectomy into a treatment option for those patients who cannot undergo transplantation [11]. The exact mechanism of splenectomy in WAS patients is not known, however, it is believed that platelet destruction is decreased and that the blocking of this clearance mechanism assists in offsetting impaired platelet production [12]. Improvement in cellular immunity had been discovered after splenectomy in WAS [13]. Post-splenectomy care followed the related guidelines, including life-long antibiotic prophylaxis and recommended immunization [14].

The mechanisms underlying the formation of nephropathy in WAS are speculative. Firstly, one hypothesis involves abnormalities in IgA glycosylation, such

as is found in IgA nephropathy [3,6]. Shimizu et al observed aberrant IgA production in WASP deficient mice and indicate that the increased IgA production and aberrant glycosylation of IgA may be critically involved in the pathogenesis of glomerulonephritis in WAS [15]. Secondly, defective glycosylation of sialophorin, which is involved in T-cell activation, and mutations in *WASP*, resulting in defective actin polymerization in hematopoietic cells, may lead to immune deficiency and recurrent infections which further increase circulating IgA [2]. Thirdly, a defective reticuloendothelial phagocytosis of IgA-containing immune complexes would enhance more immune complexes trapped in mesangium, thus causing a glomerulonephritis [5]. With regards to treatment for IgAN, there remains no consensus on the use of immunosuppressive agents for the progression of IgAN and for the modification of mesangial IgA deposition. Available treatment options are mostly directed at downstream immune and inflammatory events in the glomerulus and the tubulo-interstitium. However, when patients with WAS have IgAN, the use of immunosuppressive agents should be done so more carefully due to their underlying immunodeficiency and susceptibility to infections [17]. Recurrent infection and subsequently increased aberrant IgA formation which was scarcely removed by a deficient reticuloendothelial system may further enhance the development of IgAN. In our case, long-term antibiotic prophylaxis after splenectomy and the avoidance of using aggressive immunosuppressive agents seemed to be an effective treatment for WAS with nephropathy.

Conclusions

In summary, this case demonstrates that the early recognition of renal involvement, in combination with long-term antibiotic prophylaxis after splenectomy

and the avoidance of aggressive immunosuppressive agents provides a better renal outcome in WAS patients.

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Conflict of interest statement: None.

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Table 1. Clinical features of biopsy proven nephropathy associated with Wiskott-Aldrich syndrome (WAS) or X-linked thrombocytopenia (XLT)

| Patient no. | Age (years) | Gender | Clinical diagnosis | IgA level (mg/dL) | Pathologic findings | Treatment and outcome | Reference |
|-------------|-------------|--------|--------------------|-------------------|--|---|--------------|
| 1 | 2 | M | WAS | Nil | Interstitial nephritis IF: complement EM: no deposit | Transfer factor therapy Died | 4 |
| 2 | 4 | M | WAS | Nil | Chronic proliferative GN with focal crescent formation | Died due to sepsis | 4 |
| 3 | 12 | F | WAS variant | Elevated | Immune-complex GN IF: IgA and IgM, C3 EM: granular electron-dense deposits (hump-like) | Splenectomy Stable renal function | 9 |
| 4 | 46 | M | WAS | Elevated | MPGN with crescent and mesangial IgA deposits | Renal transplantation Recovered | 8 |
| 5 | 33 | M | WAS | Elevated | Membranoproliferative GN IF: negative for IgA | Renal transplantation Cellular rejection | 7 |
| 6 | 12 | M | WAS | Elevated | Membranoproliferative GN IF: IgA | Nil | 5 |
| 7 | 35 | F | WAS carrier | Normal | Diffuse proliferative GN with cellular crescent IF: IgA, fibrinogen, C3 | Conservative treatment ESRD under dialysis | 3 |
| 8 | 8 | M | XLT | Elevated | IgAN IF: IgA, C3 EM: electron-dense in mesangium | Low-dose Prednisolone Enalapril | 6 |
| 9 | 35 | M | XLT | Normal | IgAN IF: IgA, C3 EM: electron-dense in mesangium | ESRD under dialysis | 6 |
| 10 | 8 | M | WAS | Elevated | IgAN with FSGS and focal ATIN IF: IgA, C3 | Splenectomy Stable renal function | Present case |

IgA (normal, 79 to 169 mg/dL); Nil: no data ; GN: glomerulonephritis ; MPGN: Mesangial proliferative glomerulonephritis; ATIN: Acute tubulointerstitial nephritis ; IF: immunofluorescence; EM: Electron microscopy; IgAN: IgA nephropathy; FSGS: focal segmental glomerulosclerosis.

Legends to Figures

Fig.1 a

Light microscopy shows extensive mesangial proliferation and interstitial lymphocyte infiltrates, and focal interstitial fibrosis (H& E stain x 200).

Fig. 1 b

The immunofluorescence microscopy demonstrates granular depositions of immunoglobulin A in mesangial area (Original magnification x 200).

Fig. 2

Clinical course of the present patient. Proteinuria and renal function improved after splenectomy and the administration of long-term antibiotic prophylaxis.