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NEPHROLOGY – CASE REPORT

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. Here 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). 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.

Keywords Antibiotic prophylaxis · IgA nephropathy · Splenectomy · Wiskott–Aldrich syndrome

Abbreviations

WAS	Wiskott–Aldrich syndrome
IgAN	IgA nephropathy
XLT	X-linked thrombocytopenia
WASP	WAS protein
MPGN	Membranoproliferative glomerulonephritis
ESRD	End-stage renal disease

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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 κB 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/mm^3; and platelets, 11,000 cells/mm^3. 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 1,070 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 lifelong 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 2 years of follow-up (Fig. 2).

Discussion

The pathogenesis of WAS-associated nephropathy remains unclear, because such nephropathy is underrecognized 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. [4] described its occurrence in 6 of 32 patients. Standen [1] observed nephropathy in 4 of 13 males with XLT, thought to be a variant of WAS. 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, and 10), including our case,

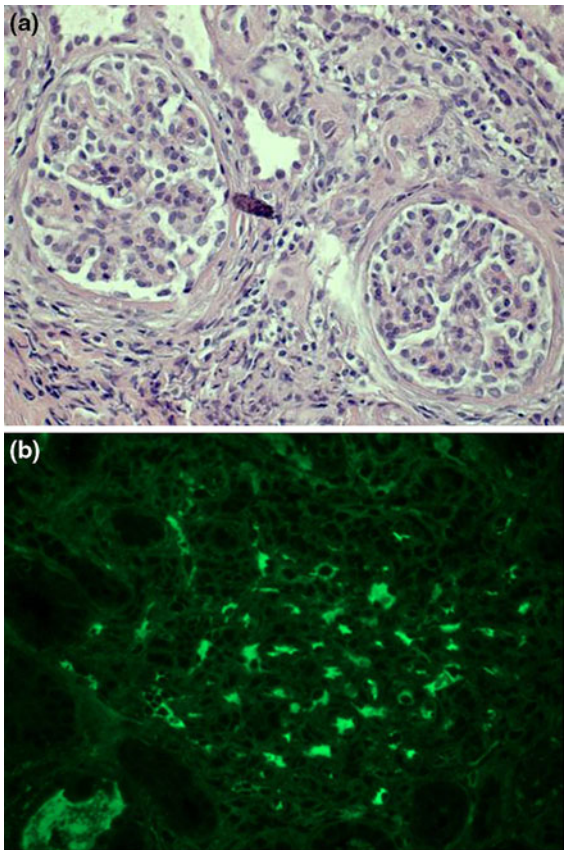

Fig. 1 **a** Light microscopy shows extensive mesangial proliferation and interstitial lymphocyte infiltrates, and focal interstitial fibrosis (H & E stain ×200). **b** The immunofluorescence microscopy demonstrates granular depositions of immunoglobulin A in mesangial area (Original magnification ×200)

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. [10] 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. 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 lifelong 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. [15] 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. Secondly, defective glycosylation

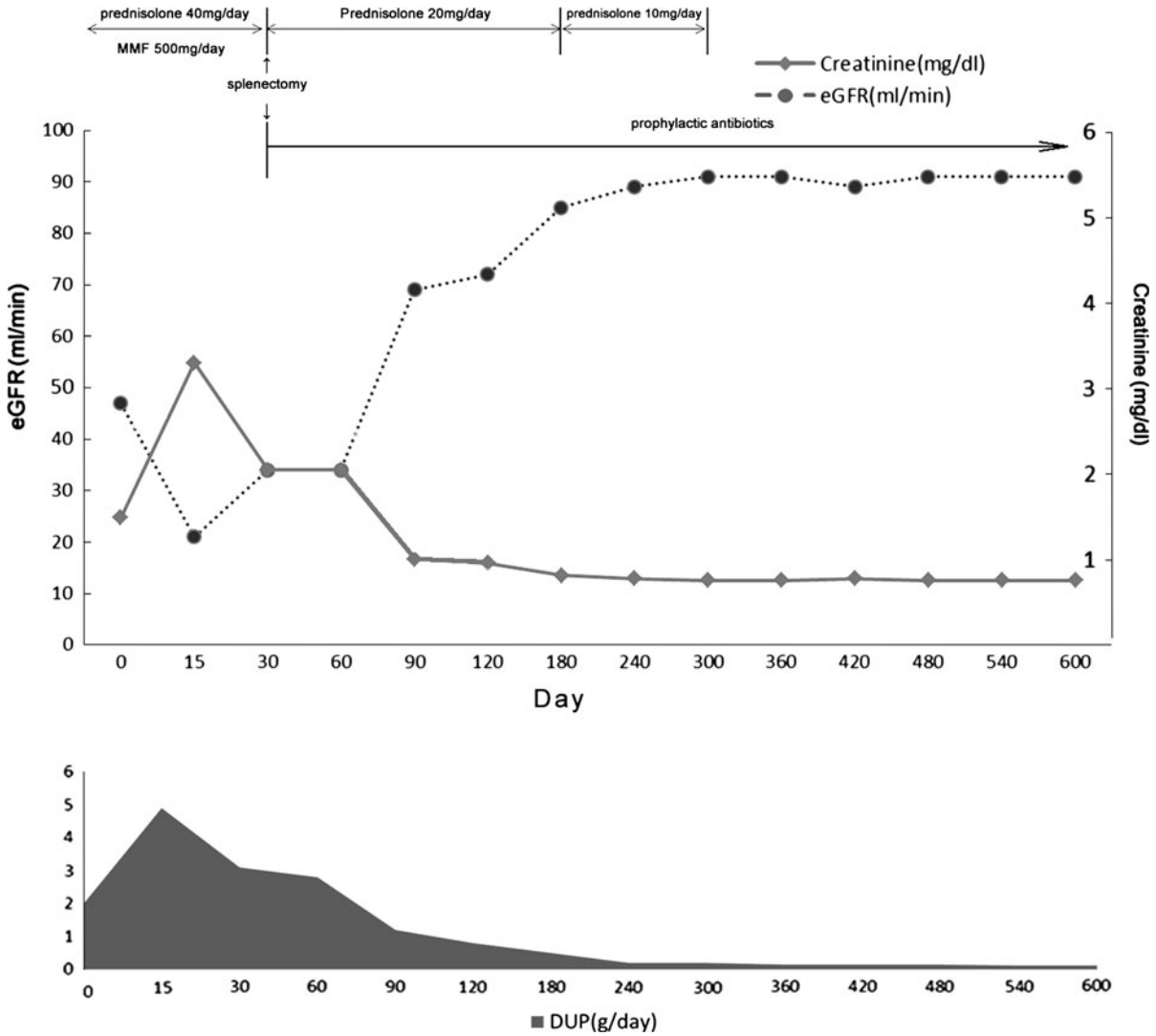

Fig. 2 Clinical course of the present patient. Proteinuria and renal function improved after splenectomy and the administration of long-term antibiotic prophylaxis

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 regard 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 [16]. 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 that 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.

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, 79–169 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

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 None.

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