Pediatric Nephrology (2023) 38:2873–2876
https://doi.org/10.1007/s00467-022-05833-6

BRIEF REPORT

Membranous nephropathy in a female patient with X-linked thrombocytopenia

Mari Okada[1] · Masayuki Nagasawa[1] · Akihiro Oshiba[1] · Hiroyuki Kawaguchi[2]

Received: 26 August 2022 / Revised: 28 October 2022 / Accepted: 16 November 2022 / Published online: 30 November 2022
© The Author(s), under exclusive licence to International Pediatric Nephrology Association 2022

Abstract

Background Wiskott–Aldrich syndrome (WAS) is an X-linked immunodeficiency characterized by thrombocytopenia and eczema and is caused by a mutation in the *WAS* gene. WAS has heterogeneous clinical manifestations, and its clinically milder form is called X-linked thrombocytopenia (XLT). Patients with WAS/XLT sometimes have kidney complications, the most common of which is immunoglobulin (Ig)A nephropathy associated with aberrant glycosylation of IgA.

Case diagnosis/treatment The patient was a 6-year-old girl who was diagnosed with female XLT at the age of 4 years; she presented with microscopic hematuria and proteinuria at a school urinalysis. Her father had thrombocytopenia and IgA nephropathy while in his 20 s. The patient and her father had the same *WAS* gene mutations. A kidney biopsy was performed, and no abnormal findings were observed by light microscopy. Immunofluorescence analysis revealed a granular pattern of IgG staining along the capillary wall. Electron microscopy revealed small electron-dense deposits in subepithelial lesions. Consequently, we diagnosed her with membranous nephropathy (MN). Tissue PLA2R and THSD7A were negative, and she was judged unlikely to have secondary MN on the basis of blood test findings and IgG staining. We started the administration of angiotensin-converting enzyme inhibitors, and her proteinuria gradually decreased.

Conclusion To our knowledge, this is the first report of MN in a female WAS/XLT patient. WAS protein expression defects affect all immune system cells; however, the mechanisms underlying the occurrence of autoimmunity are not completely understood. In WAS/XLT patients, MN may develop as a result of increased autoantibody production, similar to other types of immunodeficiency.

Keywords X-linked thrombocytopenia · Wiskott–Aldrich syndrome · Membranous nephropathy · X-inactivation

Introduction

Wiskott–Aldrich syndrome (WAS) is an X-linked immunodeficiency characterized by small platelets, thrombocytopenia, and eczema and is caused by a mutation in the *WAS* gene and deficient WAS protein (WASP) [1]. The clinical presentation of WAS is heterogeneous and ranges from a clinically mild form termed X-linked thrombocytopenia (XLT) to the classic severe immunodeficient form of WAS. XLT patients have less eczema and immunodeficiency [2]. Patients with WAS or XLT sometimes have autoimmune diseases with kidney complications, and the most common kidney disease is immunoglobulin (Ig) A nephropathy [3]. Because aberrant glycosylation of IgA has been observed in WAS patients, galactose-deficient IgA is attributed to the occurrence of kidney disease in WAS/XLT patients [4]. To our knowledge, only one case of MN in a patient with WAS/XLT has been reported [5]. Moreover, autoimmune manifestations in a female patient with WAS/XLT have not yet been reported. Here, we report the first case of a female XLT patient with hematuria and proteinuria, which was diagnosed as MN on the basis of pathological findings.

Case report

The patient was a 6-year-old girl who had had thrombocytopenia since the neonatal period but without a history of eczema or severe infection. Shortly after birth, the

✉ Mari Okada
okada-mr@musashino.jrc.or.jp

[1] Department of Pediatrics, Musashino Red Cross Hospital, 1-26-1 Kyonan-Cho, Musashino, Tokyo, Japan

[2] Department of Pediatrics, National Defense Medical College Hospital, 3-2 Namiki, Tokorozawa, Saitama, Japan

neonatologist performed a blood test because the patient had some vesicles on her skin; her platelet counts were around 50,000/μL. The vesicles were diagnosed as incontinence of pigment. The patient was observed, and the thrombocytopenia was not treated because she was not prone to hemorrhage. Her family history indicated that her father had thrombocytopenia and IgA nephropathy. The patient's mother and younger sister had no history of thrombocytopenia. During his childhood, the father's platelets ranged from 50,000/μL to 150,000/μL. He was diagnosed with chronic idiopathic thrombocytopenia and was observed. At the age of 25 years, he had nephrotic syndrome with hematuria and underwent a kidney biopsy. Pathohistological examination of nine glomeruli revealed five with mesangial hypercellularity and four with fibrocellular crescents. Immunofluorescence analysis showed diffuse mesangial IgA depositions, and electron microscopy demonstrated electron-dense deposits in the mesangial area. He was diagnosed with IgA nephropathy and underwent tonsillectomy and was given pulse steroid therapy. He still had persistent proteinuria (urine protein to creatinine ratio, 0.88 g/gCre) at age 32 years because of his poor adherence to medication. His latest estimated glomerular filtration rate was 50.8 mL/min/1.73 m^2.

At 3 years of age, the patient had purpura and further deterioration of platelets to 10,000/μL. Given her lack of response to intravenous Ig administration and her small platelet count, as well as her family history, we suspected hereditary thrombocytopenia. A genetic investigation revealed that the patient and her father had the same mutations in the *WAS* gene (c.1090C > T, c.1091_1093delGAGinsTGA, and c.1097delG). One of the three mutations (c.1090C > T [p.Arg364Ter]) has been previously reported as pathogenic for XLT [6]. Flow cytometric analysis of peripheral lymphocytes revealed markedly decreased WASP expression in both T and B cells, suggesting skewed X-chromosome inactivation. Therefore, the patient was diagnosed with female XLT. Although scheduled for periodic urinalysis, she did not undergo the follow-up. At 6 years of age, she came to our hospital again after presenting with microscopic hematuria (urinary red blood cells > 100/high power field) and proteinuria (urine protein to creatinine ratio, 1.14 g/gCre) at a school urinalysis. She did not have any symptoms such as edema, and her blood pressure was normal. Serum creatinine was 0.41 mg/dL, and the estimated glomerular filtration rate calculated using the fifth-order formula of the Japanese Society of Nephrology [7] was 102.14 mL/min/1.73 m^2. Platelet count was 105,000/μL, and the mean platelet volume was 7.6 fL. She had slightly mild hypoalbuminemia and hyperlipidemia (serum albumin, 3.3 g/dL; total cholesterol, 253 mg/dL). IgG, A, and M levels were normal (IgG, 698.8 mg/dL; IgA, 163.2 mg/dL; IgM, 119.8 mg/dL), and she did not have hypocomplementemia. Autoantibodies were negative, such as anti-nuclear antibody and perinuclear and cytoplasmic antineutrophil cytoplasmic antibodies. Furthermore, hepatitis B virus antigen and hepatitis C virus antibody were negative. She was suspected to have IgA nephropathy, and a percutaneous kidney biopsy was performed. Unexpectedly, light microscopy identified no mesangial, endocapillary, or extracapillary proliferation, sclerosis, or adhesion in 17 glomeruli (Fig. 1a). There was no deposition of IgG, IgA, IgM, C3, C1q, or fibrinogen by immunofluorescence analysis. Electron microscopy revealed small electron-dense deposits in subepithelial lesions without thickening of the glomerular basement membrane in four glomeruli (Fig. 1c). We then repeated the immunofluorescence analysis; this revealed a granular pattern of IgG staining (1 +) along the surface of the capillary wall (Fig. 1b). Additional immunofluorescence analysis showed that tissue M-type phospholipase A2 receptor (PLA2R) and thrombospondin type-1 domain-containing 7A (THSD7A) were negative, and IgG subclass staining

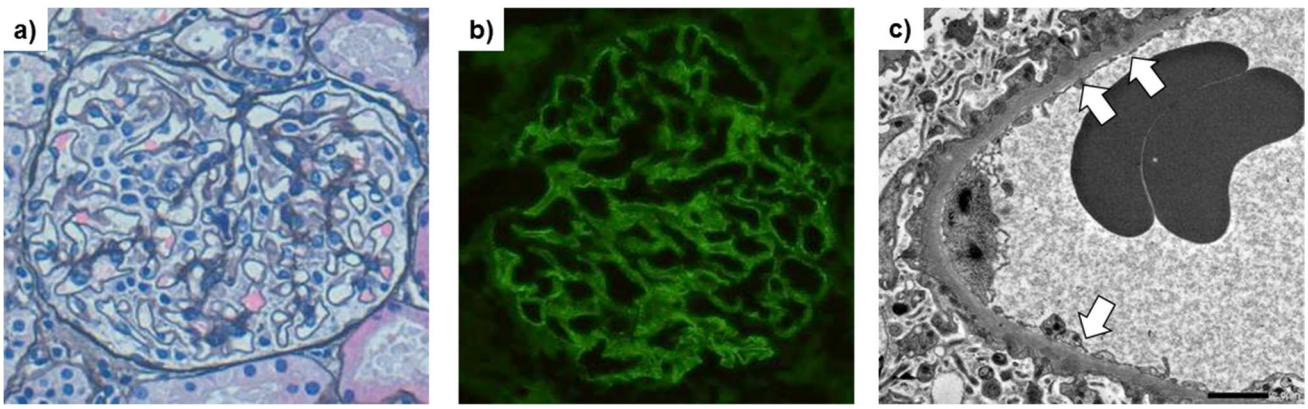

Fig. 1 Histopathological findings. **a** Light microscopy (PAM staining) showing no obvious abnormalities. **b** Immunofluorescence showing a granular pattern of IgG staining along the surface of the capillary wall. **c** Electron microscopy showing small electron-dense deposits in subepithelial lesions (white arrows)

revealed IgG1 2+, IgG2 1+, IgG3 2+, and IgG4 2+. We were unable to perform biopsy stains of other antigens such as exostosins 1 and 2 (EXT1/EXT2), neural epidermal growth factor-like 1 protein (NELL-1), neural cell adhesion molecule 1 (NCAM1), and semaphorin 3B (SEMA3B). However, in accordance with blood test findings and the results of IgG subclass staining, the patient was unlikely to have secondary MN. Upon receiving the results of the light microscopy analysis and the first immunofluorescent stain, the patient's proteinuria increased to about 1.5 g/gCre, and her serum albumin decreased to 2.7 g/dL; we therefore started her on prednisolone. However, based on the electron microscopic findings and the second immunofluorescence analysis, the diagnosis was changed to asymptomatic idiopathic MN, and angiotensin-converting enzyme inhibitors (ACEI) were administered instead of prednisolone. Her proteinuria gradually reduced to a urine protein to creatinine ratio of 0.5 g/gCre after 8 months.

Discussion

To our knowledge, only one case of MN in a patient with WAS/XLT has been reported [5]. The previous case was a 15-year-old male WAS patient diagnosed with nephrotic syndrome with MN. He was suspected to have a persistent Epstein–Barr virus (EBV) infection because of elevated titers of anti-EBV antibodies. Although we did not perform an anti-EBV antibody test in the present case, our patient did not have symptoms suggesting a persistent EBV infection.

Other reported histopathological patterns of WAS/XLT patients with kidney involvement include IgA nephropathy, membranoproliferative glomerulonephritis, mesangial proliferation, and interstitial nephritis [3]. Additionally, complications of MN have been reported in immunodeficient patients other than WAS. In a report of 22 common variable immunodeficiency (CVID) patients who underwent a kidney biopsy, 12 patients had immune complex glomerulopathy, including nine MN cases, which was the most predominant pathological finding [8]. All MN cases were negative for PLA2R and THSD7A. There was no gender difference in the prevalence of kidney involvement in CVID patients. Autoimmunity is observed in patients with CVID in addition to WAS/XLT patients, and several possible mechanisms of autoimmunity, including MN, in CVID patients have been proposed. First, B cell receptor-editing defects lead to loss of checkpoint control. Autoreactive B cell clones escape apoptosis under these defects. Additionally, there are T cell defects that lead to impaired $CD4^+$ T cell activation and depletion of regulatory T cells. Consequently, it is believed that autoimmune diseases such as nephritis occur in CVID patients because of an inability to suppress the autoimmune response [8]. Similarly, defective WASP can cause functional defects in immune system cells such as T cells, natural killer cells, regulatory T cells, and B cells. Peripheral blood regulatory T cell counts are comparable between WAS patients and healthy individuals; however, WASP-deficient regulatory T cells have an impaired ability to terminate proliferation of activated effector T cells [9]. Furthermore, it is believed that WAS patients have B cell dysfunction that leads to inadequate elimination of pathogens and chronic immune activation [10]. Additionally, in WAS patients, decreased expression of complement receptors CD21 and CD35 impairs negative selection of autoreactive B cells and increases autoantibody production [11]. In the present case, WASP expression in T and B cells was decreased uniformly, suggesting increased autoantibody production and that immune complexes may have been deposited on the basement membrane and caused MN, as occurs in CVID patients.

Although the most common clinical feature of MN is proteinuria, children with MN present with hematuria more often than adults. A review of MN in children noted that the majority of patients have proteinuria associated with microscopic hematuria; the incidence of macroscopic hematuria is approximately 40% [12, 13]. Microscopic hematuria was also identified in the present case.

Several female cases of WAS/XLT with clinical symptoms have been reported [14, 15]. In these previous reports, a random pattern of X-chromosome inactivation or skewed X-chromosome inactivation was detected. Although a genetic analysis of X-chromosome inactivation is currently underway for the present case, the finding that the patient and her father had the same mutations in the *WAS* gene and the marked impairment in WASP expression suggests that the patient had skewed X-chromosome inactivation. In previous studies, autoimmunity in female WAS/XLT has not been reported. Therefore, the prevalence of autoimmunity including nephritis in female WAS/XLT is unknown and needs to be investigated.

Generally, spontaneous remission is common, and kidney failure is rare in pediatric MN compared with adult MN [12, 13]. Therefore, pediatric MN patients may not require immunosuppression therapy unless they have severe symptoms. Hence, we decided to administer ACEI instead of prednisolone to our patient. A previous report of adult MN indicates that steroids alone show no benefits compared with conservative therapy in idiopathic MN [13]. Although prednisolone was administered for a short period in our case, the patient's proteinuria did not decrease at all in response to this treatment. Moreover, it has been reported that MN patients recover slowly, and complete remission requires many months to several years [13]. After 8 months of ACEI treatment, the patient has not yet achieved complete remission. It is unclear whether this case will follow the same

course as typical pediatric idiopathic MN, and careful observation is considered necessary.

In conclusion, we have reported the first case of MN complicated with female XLT. Kidney complications can develop even in female patients. Although IgA nephropathy and membranoproliferative glomerulonephritis have been mainly reported to be kidney complications of WAS/XLT, it is important to confirm the diagnosis by a kidney biopsy to determine a treatment plan. In the present case, proteinuria decreased after administration of ACEI. However, it is unknown whether the prognosis of this patient is comparable with that of MN patients in general, because the mechanism by which MN developed in this case is unclear.

Acknowledgements The authors thank Drs. Kenichiro Miura and Shigeru Horita for pathological examination of this case; Drs. Kohsuke Imai, Kunio Miyake, Kay Tanita, Kanako Mitsui, and Etsushi Tomifuku for immunological and genetic analyses; and Mr. Mitchell Arico and Dr. Bronwen Gardner from Edanz (https://jp.edanz.com/ac) for editing a draft of this manuscript.

Author contribution MO was involved in patient care and wrote the manuscript. MN supervised this case and contributed to critical revision of the manuscript. AO contributed to critical revision of the manuscript. HK conducted the patient's genetic analysis. All authors read and approved the final manuscript.

Data availability Not applicable.

Declarations

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Informed consent was obtained from the patient's parents.

Competing interests The authors declare no competing interests.

References

1. Ochs HD, Thrasher AJ (2006) The Wiskott-Aldrich syndrome. J Allergy Clin Immunol 117:725–738. https://doi.org/10.1016/j.jaci.2006.02.005
2. Ochs HD, Filipovich AH, Veys P, Cowan MJ, Kapoor N (2008) Wiskott-Aldrich syndrome: diagnosis, clinical and laboratory manifestations, and treatment. Biol Blood Marrow Transplant 15:84–90. https://doi.org/10.1016/j.bbmt.2008.10.007
3. Sudhakar M, Rikhi R, Loganayhan SK, Suri D, Singh S (2021) Autoimmunity in Wiskott-Aldrich syndrome: updated perspectives. Appl Clin Genet 14:363–388. https://doi.org/10.2147/TACG.S213920
4. Shimizu M, Kanegane H, Wada T, Motoyoshi Y, Morio T, Candotti F, Yacie A (2013) Aberrant glycosylation of IgA in Wiskott-Aldrich syndrome and X-linked thrombocytopenia. J Allergy Clin Immunol 131(587–590):E3. https://doi.org/10.1016/j.jaci.2012.08.040
5. Ariga T, Takahashi Y, Watanabe T, Tsuneta T, Takekoshi Y, Sakiyama Y, Matsumoto Ishii T (1986) Membranous glomerulonephritis in Wiskott-Aldrich syndrome. Pediatr Int 28:226–231. https://doi.org/10.1111/j.1442-200X.1986.tb00721.x
6. Liu H, Wang Y, Li Y, Tao L, Zhang Y, He X, Zhou Y, Liu X, Wang Y, Li L (2021) Clinical and genetic analysis of 2 rare cases of Wiskott-Aldrich syndrome from Chinese minorities: two case reports. Medicine 100:e25527. https://doi.org/10.1097/MD.0000000000025527
7. Uemura O, Nagai T, Ishikura K, Ito S, Hataya H, Gotoh Y, Fujita N, Akioka Y, Kaneko T, Honda M (2014) Creatinine-based equation to estimate the glomerular filtration rate in Japanese children and adolescents with chronic kidney disease. Clin Exp Nephrol 18:626–633. https://doi.org/10.1007/s10157-013-0856-y
8. Caza TN, Hassen SI, Larsen CP (2020) Renal manifestations of common variable immunodeficiency. Kidney360 1:491–500. https://doi.org/10.34067/KID.0000432020
9. Massaad MJ, Ramesh N, Geha RS (2013) Wiskott-Aldrich syndrome: comprehensive review. Ann N Y Acad Sci 1285:26–43. https://doi.org/10.1111/nyas.12049
10. Westernburg L, Larsson M, Hardy SJ, Fernandez C, Thrasher AJ, Severinson E (2005) Wiskott-Aldrich syndrome protein deficiency leads to reduced B-cell adhesion, migration, and homing, and a delayed humoral immune response. Blood 105:1144–1152
11. Erdei A, Isaak A, Torok K, Sandor N, Kremlitzka M, Prechl J, Bajtay Z (2009) Expression and role of CR1 and CR2 on B and T lymphocytes under physiological and autoimmune conditions. Mol Immunol 46:2767–2773. https://doi.org/10.1016/j.molimm.2009.05.181
12. Menon S, Valentini RP (2010) Membranous nephropathy in children: clinical presentation and therapeutic approach. Pediatr Nephrol 25:1419–1428. https://doi.org/10.1007/s00467-009-1324-5
13. Safar-Boueri L, Piya A, Beck LH Jr, Ayalon R (2021) Membranous nephropathy: diagnosis, treatment, and monitoring in the post-PLA3R era. Pediatr Nephrol 36:19–30. https://doi.org/10.1007/s00467-019-04425-1
14. Andreu N, Pujol-Moix N, Martinez-Lostao L, Oset M, Muniz-Diaz E, Estivill X, Volpini V, Fillat C (2003) Wiskott-Aldrich syndrome in a female with skewed X-chromosome inactivation. Blood Cells Mol Dis 31:332–337. https://doi.org/10.1016/s1079-9796(03)00168-2
15. Inoue H, Kurosawa H, Nonoyama S, Imai K, Kumazaki H, Matsunaga T, Sato Y, Sugita K, Eguchi M (2002) X-linked thrombocytopenia in a girl. Br J Haematol 118:1163–1165. https://doi.org/10.1016/j.bcmd.2013.04.004

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Springer Nature or its licensor (e.g. a society or other partner) holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.