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Immune-Negative Focal Segmental Nephrotic Syndrome Disclosing a Novel Mutation of Autosomal Dominant Alport's in a Female

Kamel El-Reshaid[1*], Abdulmohsen Al-Bader[2], Dana Al-Bader[3]

[1]Department of Medicine, Faculty of Medicine, Kuwait University, Kuwait City, Kuwait
[2]Department of ENT & ICU, Farwaniya Hospital, Ministry of Health, Kuwait City, Kuwait
[3]Department of Ophthalmology, Al-Bahar Sabah Center, Ministry of Health, Kuwait City, Kuwait
Email: *kamel@hsc.edu.kw

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Abstract

Background: Alport syndrome (AS) is a rare genetic disease characterized by progressive renal failure due to glomerulopathy, variable high-frequency sensorineural deafness, and variable ocular anomalies. **The case**: A 33-year-old woman was referred for evaluation of progressive lower limb oedema for 2 weeks following 1 week after receiving the second dose of the Oxford–AstraZeneca COVID19 vaccine. She had hypertension, hematuria, and nephrotic syndrome with serum albumin at 19 g/L and 6 g/day proteinuria. Her parents did not have renal disease. She had no clinical, laboratory, radiological, or serological evidence of autoimmune disease or infections. Kidney biopsy showed focal and segmental glomerulosclerosis with negative immunostains, yet electron microscopy showed a basket-weave appearance of the glomerular basement membrane. Genetic testing disclosed an autosomal pattern with a novel pathogenic mutation in COL4A3 c.3829G>A p.(Gly1277Ser), and COL4A5 had a c.4436C>T sequence change, replacing alanine with valine at codon 1479 protein (p.Ala1479Val). She did not respond to 2 months of therapy with diet, Losartan, and diuretics (Furosemide and Spironolactone). Since acute nephrotic state was present, Mycophenolate mofetil and Tacrolimus were selected for treatment. By 1 month later, her proteinuria decreased to 1.9 g/day, and serum albumin increased to 34 g/L. By 5 months (3 months after Mycophenolate mofetil and Tacrolimus therapy), proteinuria reached 870 mg/day and serum albumin reached 39 g/L. Hence, these were replaced by yearly Rituximab infusions. Up to 2 years of follow-up, the patient remained clinically stable and with normal serum creatinine, albumin, and proteinuria at 530 mg/day. **Conclusion**: A new-onset and novel mutation of AS can present with nephrotic syndrome after a trigger that was amenable to immunosuppressive

therapy. The genetic disorder may not be cured, yet autoimmunity may have a role in its acute flares in certain phenotypes.

Keywords

Alport Syndrome, Hematuria, Genetic Disease, Mycophenolate Mofetil, Nephrotic Syndrome, Rituximab, Tacrolimus, Triggers, Vaccination

1. Introduction

Alport syndrome (AS) is an inherited disorder that is characterized by progressive renal failure due to glomerulopathy, variable high-frequency sensorineural deafness, and variable ocular anomalies [1]. It is a heterogeneous genetic disorder, with all forms resulting in mutations in genes encoding type IV collagen (COL4A3, COL4A4, and COL4A5), which is a major structural component of the cellular basement membrane. AS is a rare disorder affecting 1 in 50,000 newborns and accounts for 0.6% of patients with end-stage renal disease (ESRD) [2]. It has 3 types of inheritance that differ in severity and affected organs: (a) X-linked (COL4A5 gene), which is the most common (80%), leading to severe classic disease in males; (b) autosomal recessive (homozygous or compound heterozygous mutations in COL4A3/4 genes), which can present with severe classic disease affecting both genders equally while both their parents are healthy carriers; and (c) autosomal dominant (heterozygous mutations in COL4A3/4 genes), which is extremely rare, affects both genders, and requires one parent carrier [3]. In X-linked AS, all affected males present with severe disease, whereas only 12% of females with a heterozygous mutation progress to kidney failure due to X-chromosome inactivation [4]. Renal involvement in AS manifests with microscopic hematuria and slowly progressive renal failure [5]. Nephrotic-range proteinuria and nephrotic syndrome, with podocytopathy, were reported only in 2 cases, of heterogeneous AS mutations with early (6 & 15 years) and aggressive disease [6] [7]. In this case report, we present a rare presentation of a new mutation leading to acute nephrotic syndrome due to an autosomal disease in a female and discuss its management and implications.

2. The Case

A 33-year-old woman was referred for evaluation of progressive lower limb oedema for 2 weeks. She did not have a past history of chronic diseases, autoimmune disorders, or long-term drug use. There was no documented renal disease in her parents, yet 2 of her 4 children (a boy & a girl) have microscopic hematuria. She had just received the second dose of the Oxford–AstraZeneca COVID-19 vaccine 1 week before. On physical examination, she had puffy eyelids and moderate sacral as well as lower limb oedema. She was afebrile yet hypertensive (160/105 mm Hg), without lymphadenopathy or raised jugular venous pressure. Her weight

was 81 kg. Systemic examination did not show abnormality. Laboratory abnormalities showed normal peripheral leucocyte and platelet counts as well as hemoglobin. Serum sugar, urea, creatinine, electrolytes, and liver function tests were normal except for low albumin at 19 g/L. Urine testing revealed (+) proteinuria and excess RBCs/HPF. Serum complements (C3 & C4), IgA, IgG4, and protein electrophoresis were normal. ANA, anti-ds DNA, ANCA, anti-streptolysin O, anti-GBM antibodies, hepatitis B surface antigen, and anti-HCV antibodies were negative. Twenty-four-hour urine showed creatinine clearance at 2.3 ml/second and protein excretion at 6 g/day. Chest X-ray and ECG were normal. Abdominal and pelvic ultrasound were normal except for increased renal cortical echogenicity. Computerized tomography scan of the chest and abdomen did not show gut or respiratory tract thickening, aortic aneurysms, or cystic/dysplastic/stone/neoplastic kidney disease. After control of hypertension with daily losartan 50 mg, control of oedema with albumin/furosemide infusions every 8 hours, and exclusion of infection, kidney biopsy was done. As seen in **Figure 1**, it showed a total of 24 glomeruli, of which none were globally sclerosed yet 3 showed segmental sclerosis. The interstitium showed mild fibrosis (10%) and a few aggregates of foam cells. Immunostains were negative. Electron microscopy showed multilamellated glomerular basement membrane (basket-weave appearance) with irregular thickening and marked effacement of the epithelial cell foot processes (**Figure 2**). Genetic testing for variations was done by high-throughput targeted next-generation sequencing (NGS) technologies [8]. Genetic tests showed a heterogeneous missense pathogenic variant in the COL4A3 gene as well as a novel missense pathogenic variant in COL4A5 (c.4436C>T sequence change), confirming the diagnosis

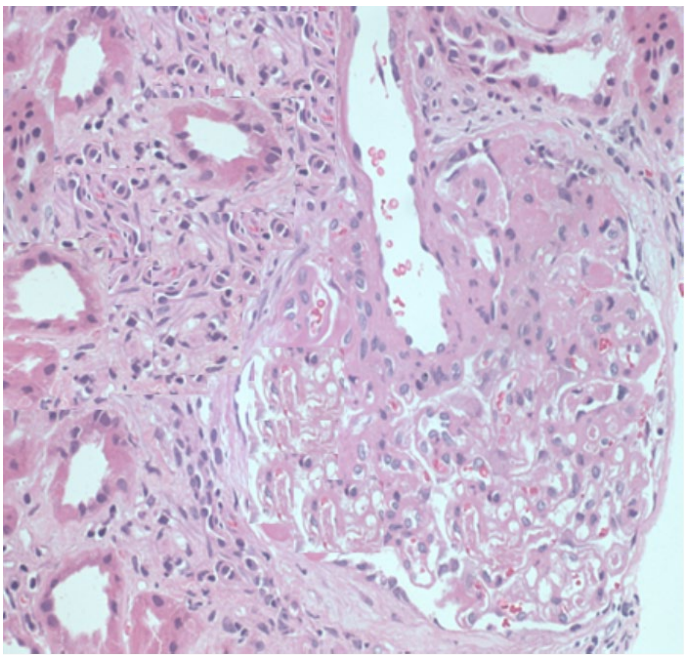

Figure 1. Photomicrograph of a kidney biopsy showing a glomerulus with segmental glomerulosclerosis (H & E ×400).

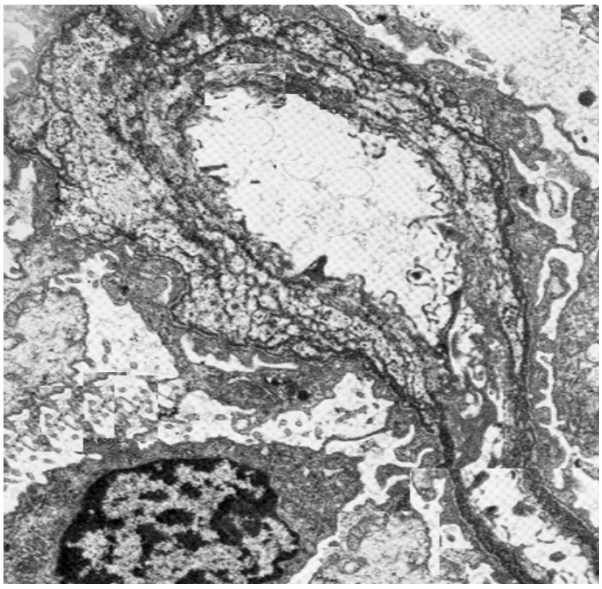

Figure 2. Photomicrograph of an electron microscopic image of a glomerulus showing (a) fragmented (basket-weave) basement membrane, and (b) effacement of the epithelial cell foot processes.

of autosomal dominant Alport syndrome. By NGS testing, the changes were COL4A3 c.3829G>A p.(Gly1277Ser) and COL4A5 c.4436C>T sequence change, which replaces alanine with valine at codon 1479 protein (p.Ala1479Val). The latter is novel and has not been reported in the genome aggregation database (gnomAD v4.1.0) or ClinVar. It is located in a hotspot of length 17 amino acids with 14 missense/in-frame variants (8 pathogenic variants, 5 uncertain variants, and 1 benign variant), which qualifies it as moderately pathogenic. After the results of the kidney biopsy, the patient was instructed to adhere to dietary restrictions (low sodium, potassium, and protein) and a combination of losartan and diuretics (furosemide 40 mg and aldactone 25 mg) daily. Unfortunately, she did not respond to such management in the subsequent 2 months. Hence, a trial of mycophenolate mofetil (MMF) 1 g twice daily and tacrolimus (T) 2 g twice daily was done. By 1 month later, her proteinuria decreased to 1.9 g/day and serum albumin increased to 34 g/L. After 3 months of induction therapy with MMF and T, proteinuria decreased to 870 mg/day and serum albumin increased to 39 g/L. Hence, rituximab (R), at a dose of 1 g followed by another 1 g two weeks later, was started as maintenance therapy, and MMF and T were tapered down and discontinued 1 month later. Up to 2 years of follow-up, the patient remained clinically stable with normal serum creatinine, albumin, and proteinuria at 530 mg/day. The demographic data and results of investigations before and after therapy are summarized in Table 1. Following such improvement, the future plan is to continue R maintenance therapy for a minimum of 4 years.

3. Discussion

As in our patient, the autosomal dominant form of AS typically has a delay in

ESRD until middle age, in contrast to X-linked and autosomal recessive ones that present at an early age [9]. However, its presentation disclosed multiple valuable data with regards to AS. Genetic testing disclosed a new disease variant. Moreover, her autosomal mode of inheritance, without parental kidney disease yet with 2 possibly affected children, qualifies her as an index case of a new AS in the family. Her disease was limited to the kidney and ears. Contrary to the most common X-linked type, such rare autosomal dominant AS can present with severe renal disease in females [10]. As described previously, nephrotic-range proteinuria and nephrotic syndrome were extremely rare, yet were reported in 2 cases [6] [7]. Our patient had a history of Covid-19 vaccination 1 week prior to her acute kidney disease, and at that time her routine tests were normal except for an overlooked microscopic hematuria (**Table 1**). Her immediate renal deterioration following COVID vaccination and her response to immunosuppressive therapy indicated autoimmunity as the culprit for it. The choice of MMF and T over corticosteroids was for (a) short- and long-term complications of corticosteroids and (b) the efficacy of MMF and T combinations in management of refractory and even steroid-resistant glomerulopathy [11]-[13]. The issue of an incidental idiopathic focal segmental glomerulosclerosis superimposed on AS is intriguing, yet the

Table 1. Flow chart of demographical data and biochemical changes of a treated patient with NS due to AD-Alport syndrome.

		Time (months)				
	-1	0	3		5	24
Age, gender & race: 33 years, female, White						
Clinical data:						
Manifestations	None	2 weeks of generalized oedema after Covid-19 vaccination				
Blood pressure: (120-80 mm Hg)	120/80	160/105	120/80	120/80	120/80	120/80
Body weight: (Kg)	72	81	76		74	74
Oedema:	None	(2+)	None		None	None
Laboratory tests:						
Hemoglobin: (130-160 g/L)	129	124	121		128	123
Serum:						
urea (4-6 mmol/L)	4	4	5		4	5
creatinine (60-120 umol/L)	65	64	110		95	98
albumin (35-50 g/L)	42	19	34		39	38
Urine routine & microscopy (blood/protein):						
(-) & (-)	(2+) & (-)	(3+) & (4+)	(2+) & (2+)		(2+) & (1+)	(2+) & (1+)
24-hour urinary protein:	ND					
(< 150 mg)		6000	1900		870	530
Creatinine clearance: (umol/L)	ND	2.1	0.9		1.1	1.1
Autoimmune tests:		Negative				
Infections (TB, EBV, $, HIV):		Negative				
kidney biopsy:		LM: FSGS, EM: basket-weave appearance of basement membrane and effacement of FP without IgM mesangial deposits				
Audiometry:		High-frequency nerve deafness				
Ophthalmological assessment:		Normal cornea and retina				
HRCT chest & upper GI endoscopy:		No esophageal leimyomata				
Genetic testing:		Novel missense pathogenic mutations in COL4A3/4A5				
Management:						
Furosemide/Aldactone						
Losartan						
Tacrolimus						
Mycophenolate mofetil						
Rituximab						

Abbreviations: NS; nephrotic syndrome, AD; autosomal dominant, TB; tuberculosis, EBV; Ebstein Barr Virus, HIV; Human immunodeficiency virus LM; Light microscopy, FSGS; Focal and segmental glomerulosclerosis, HRCT; High resolution chest computerized tomography, GI; gastrointestinal, EM; Electron microscopy, FP; Epithelial cells foot processes.

absence of IgM deposits by immunostains and electron microscopy excludes it and categorizes such changes as a secondary phenomenon akin to AS [14]. Moreover, an incidental and idiopathic minimal change disease, superimposed on AS, is possible. However, her renal disease was characterized by 1) hypertension at presentation, 2) persistent mild proteinuria despite adequate response to immunosuppressive drugs, which was not detected prior to the second vaccination, 3) evident focal and segmental sclerosis on biopsy. Such a presentation is atypical for pure minimal change disease. Up to date, there is no specific treatment for Alport syndrome. Management is focused on limiting the disease progression by lowering intraglomerular pressure through a low salt/protein diet as well as the use of ACEI or ARB [15]. Interestingly, the induction of autoimmune antibodies in AS is known. Post-renal transplantation data indicate a 3% risk of de novo anti-GBM antibody disease or Alport posttransplant nephritis in XLAS with COL4A3, with relapses in the first year due to circulating anti-GBM antibodies, leading to crescentic nephritis and recurrence after retransplantation [16]. In those patients, treatment involves plasmapheresis along with cyclophosphamide and methylprednisolone. Such autoimmune phenomena are associated with acute kidney disease flares with triggers in AS. The response in our patient following disease activation may assist in the management of similar acute events in AS patients. Moreover, it may have future long-term benefit in delay of certain patients with rapid disease progression.

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Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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