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Case Report

Review of the literature on Alport syndrome: A rare cause of nephrotic syndrome

Fahriye Secil Tecellioglu[1], Nusret Akpolat[2], Yilmaz Tabel[3], Mehmet Gul[4]

[1]Department of Pathology, Malatya Education and Research Hospital, Malatya, Turkey
[2]Department of Pathology, Faculty of Medicine, Inonu University, Malatya, Turkey
[3]Department of Pediatric Nephrology, Faculty of Medicine, Inonu University, Malatya, Turkey
[4]Department of Histology, Faculty of Medicine, Inonu University, Malatya, Turkey

Abstract

Alport syndrome is a type IV collagen synthesis disorder characterized by hereditary progressive glomerular disease resulting from glomerular basement membrane injury, often accompanied by hearing loss and ocular defects. The most common form is X-linked Alport syndrome, which accounts for 80% of all cases. Although women mainly present with mild urinary symptoms, end-stage renal disease onsets at an early age in men. An 11-year-old girl was admitted to our hospital with mild bifissure oedema for the last 3 months. This study discusses the clinical, morphological and transmission electron microscopic findings of a rare case of Alport syndrome in the context of the wider literature.

Keywords: Alport syndrome; hereditary nephropathy; nephropathology

INTRODUCTION

Alport syndrome is followed by progressive glomerular disease, which leads to progressive sensorineural hearing loss, retinal spotting, anterior lenticonus, subcapsular cataract and, in rare cases, aortic aneurysm. This is caused by mutations in the type IV collagen genes responsible for the formation of the glomerular basement membrane (GBM) (1).

The incidence of Alport syndrome in the community is 0.02%. The first clinical symptom is typically haematuria, which is commonly followed by increased proteinuria and progressive renal failure. The age of onset is variable, ranging from early childhood to middle-to-advanced age. The age at diagnosis tends to be similar among affected individuals in the same family (2).

About 80% of Alport syndrome cases are caused by mutations in the COL4A5 gene, on the X chromosome. Affected individuals typically develop end-stage renal disease. Approximately 90% of heterozygous female X-linked inherited cases experience mild urinary symptoms and haematuria (with or without age-related proteinuria) (3). The majority of cases result from mutations at the COL4A3/COL4A4 locus on chromosome 2; these cases are classified as autosomally inherited Alport syndrome (2). Contrary to cases of X-linked Alport syndrome, patients with the autosomally inherited form show renal involvement, ranging from benign urinary abnormalities to progressive nephropathy causing end-stage renal disease. Morphology is also variable in this subset of patients. In cases of autosomal recessive disease, diffuse global thinning is observed in the GBM, and thin basal membrane nephropathy (TBMN) is seen instead of lamellation and sporadic thin and thick areas (2). IgA nephropathy causing persistent haematuria is morphologically similar to TBMN, and may be used in the differential diagnosis thereof. We present this case study to promote awareness of a differential diagnosis that is rarely made in routine pathology practice.

CASE REPORT

An 11-year-old girl presented to the paediatric nephrology outpatient clinic due to mild bifissure oedema. She stated that she had no macroscopic haematuria, headache, periodic fever, abdominal pain, joint pain or rash. Her general appearance and condition were good on physical examination. Her height and weight were within the 25-50 percentile for her age group, and systemic examination revealed no pathological features. The patient had previously presented to the outpatient clinic with the

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Corresponding Author: Fahriye Secil Tecellioglu, Department of Pathology, Malatya Education and Research Hospital, Malatya, Turkey
E-mail: f.seciltecellioglu@gmail.com

same complaint 1 year ago, and had been diagnosed with proteinuria. There were no notable features in the natal or postnatal history. Regarding the family history, the patient's mother had a history of chronic renal failure (CRF) and renal transplantation. The primary cause of CRF in the mother was unknown. Her mother and father was first degree relatives. The hemogram was unremarkable. Serum biochemical analysis revealed that blood urea nitrogen (BUN), creatinine, total protein and C3, C4 and electrolyte levels were within normal limits, while the albumin level was slightly low (3 g/dL) and uric acid was slightly elevated (5.32 mg/dL). Complete urinalysis revealed score of 2+ protein and 1+ blood cells. Urine microscopy revealed 6–8 erythrocytes per high power field (HPF). Protein was detected at a "nephrotic level" (54 mg/m2/h) based on 24-hour urine collection. Ultrasonography revealed increased renal parenchymal echogenicity compatible with grade II. The right and left kidneys measured 90 × 38 and 88 × 40 mm, respectively. The mean parenchymal thickness was 7 mm. The patient was hospitalized with a preliminary diagnosis of hereditary nephritis based on clinical and laboratory findings, and ACE inhibitor medication was started. Renal biopsy was planned.

Fresh tissue was subjected to transmission electron microscopy (TEM) and direct immunofluorescence (DIF) examination. Immunofluorescence dyes (IgG, IgA, IgM, C3, C1q, kappa, lambda, and fibrinogen) were applied to the tissue samples, which were fixed with 2.5% glutaraldehyde and 1% osmium tetroxide for the TEM examination. Tissues fixed in 10% neutral formaldehyde were stained with haematoxylin-eosin (H&E) and histochemical stains (periodic acid-Schiff, periodic acid methenamine silver (, Jones methenamine silver, Masson's trichrome, Congo red) and examined under a light microscope (LM). Two of the seven glomeruli examined by LM showed global sclerosis, mild endocapillary proliferation, mesangial matrix accumulation and increased expression of glomerular cells. Segmental sclerosis and crescent formation were not observed. LM showed that the GBM was of normal thickness. In the interstitial area, there were signs of mild but chronic interstitial nephritis, mild interstitial fibrosis, tubular atrophy and thyroidisation. Diffuse mild hydropic degeneration and lipoproteinous granules were seen within the tubules. There was minimal thickening of the arteriole walls. Unfortunately, the tissue intended for DIF examination could not be evaluated due to the absence of glomeruli (Figure 1-3).

TEM revealed undulation and duplication of the lamina densa in the GBM. Both thickening (thickest part = 1,400 nm) and thinning (thinnest part = 175 nm) of the GBM were observed, while fragmentation and lamination were observed in tubular basement membranes. Mitochondrial condensation, degeneration, size and shape differences, abnormal granule deposition and hydropic degeneration were observed in proximal tubule epithelial cells. The clinical, histopathological and TEM findings were consistent with a diagnosis of Alport syndrome (Figure 4-6).

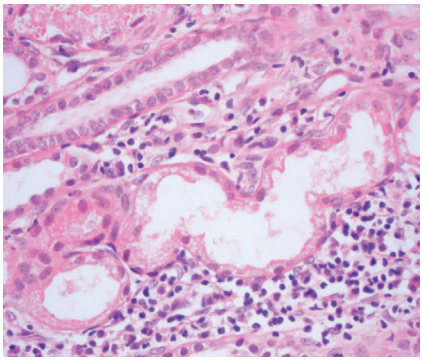

Figure 1. Tubulointerstitial inflammation and lipoproteinous granules in tubular epithelial cells (Hematoxylin Eosin x400)

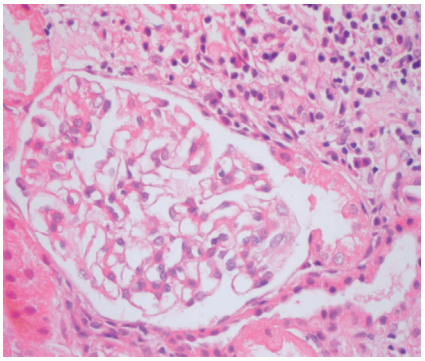

Figure 2. Regular structure of the glomeruli and tubulointerstitial inflammation [Hematoxylin Eosin x400]

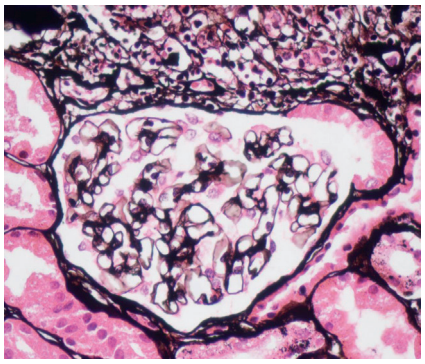

Figure 3. Regular structure of the glomeruli and tubulointerstitial inflammation [Jones Methenamin Silver x400]

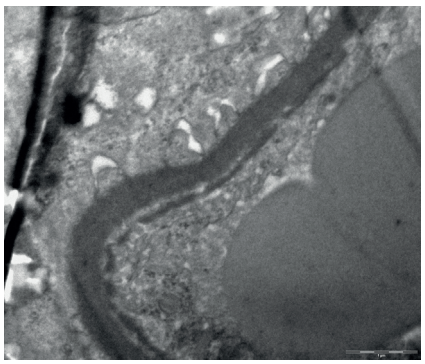

Figure 4. Lamination of glomerular basement membrane (TEM, x16000)

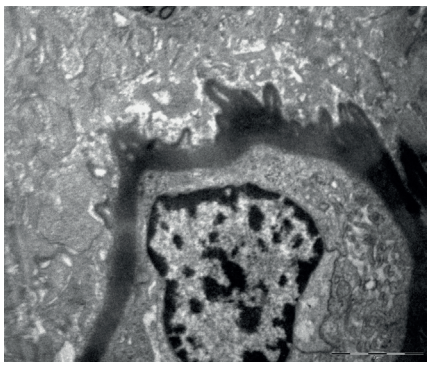

Figure 5. Duplication of the glomerular basement membrane (TEM, x10000)

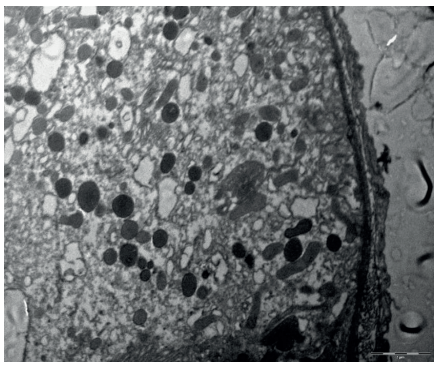

Figure 6. Increased number of mitochondria in variable size and shape and abnormal deposits in proximal tubule cells (TEM, x6300)

DISCUSSION

Alport syndrome was first defined in 1927 by Cecil Alport, who discovered an association between deafness and a form of 'hereditary familial congenital haemorrhagic nephritis' in several generations of a family (4). Alport syndrome is a genetically heterogeneous disorder: mutations in different genes encoding α3, α4 and α5 chains of type IV collagen are responsible for differences in disease morphology, with X-linked inheritance being the most common form of familial transmission. Each family is characterized by specific mutations and, due to molecular heterogeneity, the disease has a heterogeneous phenotype (4). The incidence of end-stage renal disease is 0.02% in the world. 1.9% of all cases are seen in the USA. (4).

The LM examinations in our study revealed evidence of early changes in glomeruli, podocyte hypertrophy, and capillary wall thickness, as well as enlargement of mesangial roots and focal thickening of the capsular basement membrane. Segmental involvement and diffuse GBM thickening may be seen depending on the stage of the disease. In our patient, global sclerosis and mesangial matrix accumulation were observed in glomeruli. In glomeruli without global sclerosis, we found no increase in GBM thickness. Since the cortical area and the number of full profile glomeruli of our patient were few and localized at the margin, the thickness of the GBM may not have been accurately determined by the LM examination. In Alport syndrome, there is usually no significant change in vascular structures (4).

The most prominent feature of Alport syndrome revealed by LM examinations is the presence of lipid-laden interstitial foam cells. These cells often accumulate in deep cortical areas and are characterized by "yellow streaking". Foam cells are mostly seen in older children and adults, often in association with markers of chronic disease such as glomerular sclerosis, tubular atrophy, and interstitial fibrosis (2). In our case, we observed mild but chronic inflammation of the interstitium, along with tubular atrophy, interstitial fibrosis, and global sclerosis. Inflammation was indicated by the patterns of expression of lymphocytes, plasma cells and neutrophils, but the lipid-laden interstitial foam cells commonly mentioned in the literature were not present. This could have been due to the young age of the patient, such that the interstitial space in the cortex was narrow and the biopsy area was small. We also observed widespread thyroidisation and erythrocyte casts in tubules, which are characteristic clinical findings of haematuria.

Fibrosis in the glomerular and interstitial compartments plays an important role in the progression of Alport syndrome. Another factor that contributes to the progression of this disease is a lack of ability of podocytes to adhere to the deteriorating GBM (5).

Immunoglobulins and complement proteins are not generally revealed by DIF (4). In our case, glomeruli were not revealed by DIF staining.

TEM typically reveals cleavage of the lamina densa and thickening of the GBM (800–1,200 nm); these features lead to a "fragmented mesh" appearance. The inner and outer parts of the GBM are highly irregular due to cleavage, and the outer part is also covered by hypertrophic podocytes. In adults, lesions are observed in more than 50% of capillary loops (4). In our patient, the clinical and TEM findings were ultimately more diagnostic than the LM and DIF ones. The basal membrane had both thick and thin focal regions, and duplication of the lamina densa and undulation of the GBM were observed. The symptoms supported the diagnosis of Alport syndrome.

Although extensive thickening and cleavage of the GBM strongly supports a diagnosis of Alport syndrome, infrequent GBM cleavage without other biopsy results is not sufficient to diagnose Alport syndrome (4).

Alport syndrome is genetically heterogeneous. COL4A5 mutations are common in X-linked autosomal dominant Alport syndrome, while COL4A3 and COL4A4 mutations are common in both the autosomal recessive and dominant forms (6). Type IV collagen consists of heterotrimers comprised of six different α-chains, and mutations in these genes can be revealed by DIF staining. Since the α5 subtype is normally present in the basal layer of the epidermis, there is no staining with collagen type IV-α5 subtype in skin biopsy and kidney GBM in X-linked Alport syndrome. In autosomal recessive or dominant forms,

there is no staining with α3, α4 and α5 subtypes in GBM. However, in Bowman's Capsule distal tubular basement membrane and normal staining with α5 are present in the skin (7).

TBMN and IgA nephritis should be considered in the differential diagnosis of Alport syndrome. There are many clinical and histopathological similarities between TBMN and early onset Alport syndrome. TBMN is characterized by diffuse thinning of the GBM, which can be revealed by TEM examination, as well as COL4A3/COL4A4 mutations. These features are also observed in early stage Alport syndrome, which is commonly misdiagnosed as TBMN. In previous studies, patients thought to have TBMN were ultimately diagnosed with X-linked inherited Alport syndrome after follow-up biopsies. Collagen IV immunostaining and genetic studies may be beneficial for diagnosis (8,9). IgA nephritis should also be kept in mind, because diffuse IgA DIF staining in the mesangium is a diagnostic marker of IgA nephritis. The TEM findings of IgA nephritis, which is not characterized by any change in the GBM, are very different from those of Alport syndrome. Mesangial electron-dense deposits are commonly revealed by TEM in cases of IgA nephritis. Subendothelial electron-dense deposits in active lesions may also be present (7).

CONCLUSION

In this case, LM and DIF findings were non-specific for Alport syndrome in a patient who presented with nephrotic syndrome at a young age. Alport syndrome was diagnosed based on the TEM findings. Since histopathological examination at an early age does not reveal the typical features of Alport syndrome, it is necessary to consult the medical and family histories. In cases where the diagnosis is not clear, it is very important to fix fresh tissue in glutaraldehyde solution for TEM examination.

Conflict of interest: The authors declare that they have no competing interest.

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