

Alport syndrome – a rare histological presentation

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ABSTRACT

Hereditary nephritis or Alport syndrome is a progressive form of glomerular disease that is often associated with neural hearing loss and ocular abnormalities. The histological changes in Alport kidneys are characteristic but not pathognomonic. The presence of crescentic formations is rare.

We report the case of a 16-year-old male with a family history of renal disease who underwent renal transplantation after progressive renal failure due to Alport syndrome with crescentic proliferation on renal biopsy.

Although rare, the evidence of crescentic proliferation in Alport syndrome has been documented by some authors. It is difficult to identify its role as a cause or an epiphenomenon of the evolution observed. However, when found in a renal biopsy its presence can be interpreted as a marker of unfavourable outcome and therefore identify patients at a higher risk of rapid renal function deterioration.

Key-Words:

Alport syndrome; crescentic proliferation; hereditary nephritis; kidney biopsy.

INTRODUCTION

Hereditary nephritis or Alport syndrome is a progressive form of glomerular disease that is often

associated with neural hearing loss and ocular abnormalities¹⁻⁴. The prevalence of this disease is estimated at approximately 1 in 50 000 live births⁵. Studies carried out since the 1980s have established that Alport syndrome is a primary basement membrane disorder arising from mutations in genes encoding several members of the type IV collagen protein family^{1,6,7}. It is a genetically heterogeneous disease with X-linked, autosomal recessive and autosomal dominant variants^{1,7}. In approximately 80 percent of patients the disorder is inherited as an X-linked trait, arising from mutations in the COL4A5 gene on the X chromosome¹. Autosomal recessive inheritance accounts for about 15 percent of patients with hereditary nephritis⁸. The genetic defect in these patients involves the COL4A3 and COL4A4 genes, which are located on chromosome 2¹. The clinical manifestations are virtually identical to those of classic X-linked hereditary nephritis^{9,10}. About 5 percent of families have autosomal dominant disease, which arises from heterozygous mutations in the COL4A3 or COL4A4 genes^{4,11}. The clinical and pathologic features of this form are similar to those of X-linked disease, although deterioration of renal function tends to occur more slowly^{4,12}.

The initial renal manifestation of Alport syndrome is asymptomatic microhaematuria¹. This usually begins in childhood and is manifested by recurrent or persistent haematuria and proteinuria¹³. Increasing proteinuria, hypertension and progressive renal insufficiency occur with time¹. End-stage renal disease usually presents in males in the second or third

decade, during late adolescence or early adulthood^{1,2,13}.

The diagnosis of Alport syndrome is usually suspected from the family history of renal failure and deafness¹, and can subsequently be confirmed or excluded in the majority of cases by the performance of a renal biopsy¹. On electron microscopy, the earliest change is thinning of the glomerular basement membrane (GBM)¹⁴, which is not pathognomonic¹. With time, the changes become diagnostic for Alport syndrome, with the development of longitudinal splitting of the lamina densa of the GBM, producing a laminated appearance^{1,13}. Although not absolute, there appears to be a correlation between the severity of the underlying genetic defect and the severity of the ultrastructural changes^{1,13}. The renal histological changes on light microscopy are nonspecific and include focal increases in glomerular cellularity, progressing to glomerulosclerosis, and interstitial infiltrate containing lipid-laden foam cells of uncertain origin¹. Although described in the literature¹⁵⁻¹⁹, the presence of crescentic formations in Alport syndrome is rare.

There is no specific treatment for Alport syndrome¹. Angiotensin-converting enzyme inhibitors have been used to retard the progression of the disease⁶, and they are particularly prescribed for those patients with proteinuria. Another pharmacological therapy is ciclosporin, which can suppress proteinuria and stabilise renal function and histological changes²⁰. Either dialysis or transplantation can be performed in patients who develop end-stage renal failure¹.

The objective of this case report is to present and discuss the case of a 16-year-old male with renal failure due to Alport syndrome, with crescentic proliferation on renal biopsy.

■ CASE REPORT

We report a case of a 16-year-old male who underwent renal transplantation after progressive renal failure due to Alport syndrome with crescentic proliferation on renal biopsy. His family history was significant for his mother, who presented in her late 20s with persistent haematoproteinuria. There was

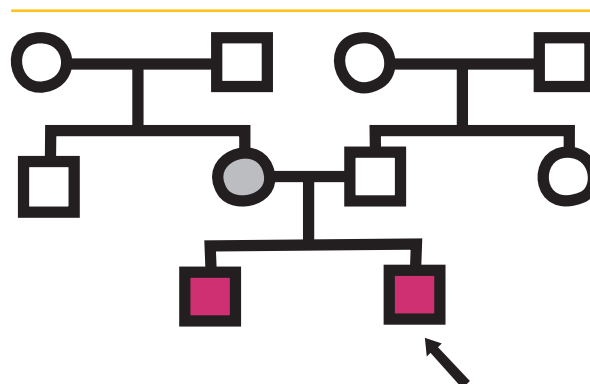


Figure 1

Pedigree of family

The arrow indicates the index patient. Filled dark squares indicate individuals with Alport syndrome. Filled light circle indicates individual with haematoproteinuria.

also an older brother with Alport syndrome diagnosed at the age of seven (Fig. 1).

The patient presented initially with glomerular microscopic haematuria when he was six months old. Recurrent episodes of macroscopic haematuria were noticed after nine months of age. Haematoproteinuria was documented at the age of three and he started on angiotensin-converting enzyme inhibitor. Long standing haematuria and intermittent proteinuria have been documented since then. The immunological study was normal, including complement component levels, antinuclear antibodies, anti GBM antibodies and MPO-ANCA and PR3-ANCA. Sensorineural hearing loss was detected when he was nine, and a hearing aid was provided. He has been under regular ophthalmologic surveillance, without significant alterations. He developed nephrotic syndrome at the age of 10 years, with a quantified proteinuria of 99mg/m²/hour and a glomerular filtration rate (GFR) of 107ml/min/1.73m² of body surface area and normal blood pressure, resulting in ciclosporin being introduced. Treatment with ciclosporin was maintained for four years, with progressive reduction of the dose. He had good response, with decreasing urinary protein excretion and stable creatinine clearance until he was 14. Blood pressure always remained within normal ranges for age and gender.

At 15 years old, approximately one year after ciclosporin had been discontinued, sudden

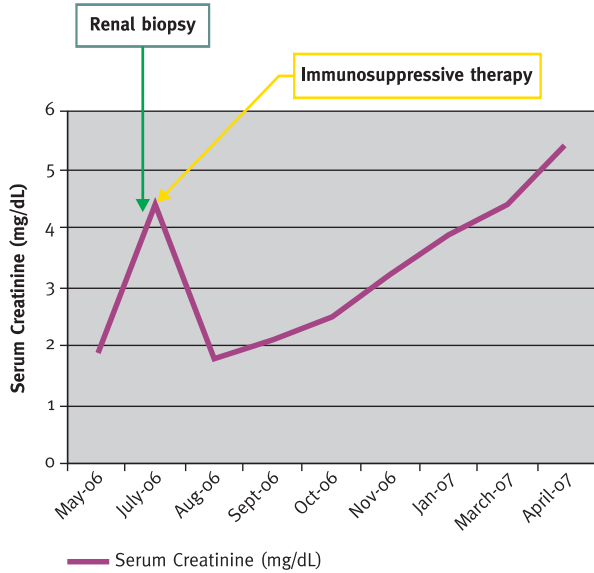
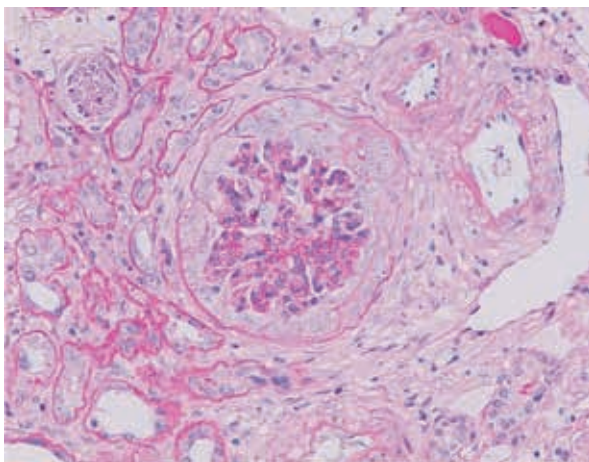


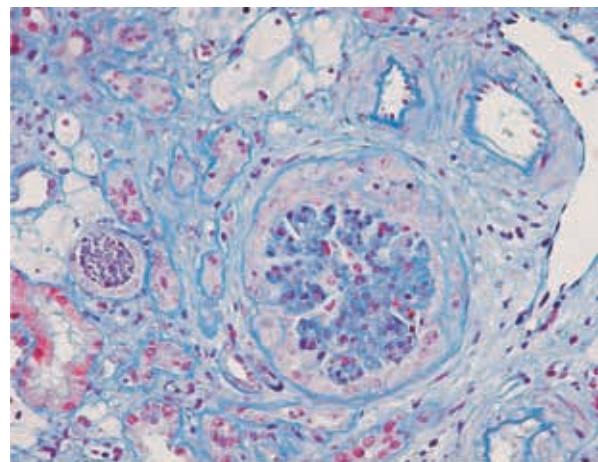
Figure 2
Renal function before and after renal biopsy and response to immunosuppressive therapy.

deterioration of renal function was noticed. In a few weeks, his serum creatinine rose from near normal values (1.9mg/dL) to 4.4mg/dL (Fig. 2) and so it was decided to perform a renal percutaneous

needle biopsy. The biopsy specimen consisted of renal cortex with 15 glomeruli per level section. It showed focal increases in glomerular cellularity with crescentic proliferation, corresponding to 20% of glomeruli. An additional 13% of glomeruli showed segmental sclerosis. Interstitial infiltrate containing lipid-laden foam cells on light microscopy was seen (Fig. 3). The ultrastructural examination showed diffuse and markedly abnormal architectural organisation of the GBM, characterised by a lamellated appearance and longitudinal splitting of the lamina densa; some immune-type electron-dense deposits were identified (Fig. 4). It was not possible to perform immunofluorescence staining of the specimen because the sample was insufficient. The diagnosis of Alport syndrome was definitively established with additional features of focal cellular crescent formation. Due to sudden deterioration of his renal function immunosuppressive therapy was started (three pulses of IV methylprednisolone 7.5mg/kg/day followed by 30mg/day of oral prednisolone, associated to oral cyclophosphamide 2mg/kg/day). Transient recovery occurred (Fig. 2). Despite all the efforts, less than 12 months later he showed further deterioration of renal function with progression to end-stage kidney disease. He needed haemodialysis less than a month later and underwent renal transplantation soon after.

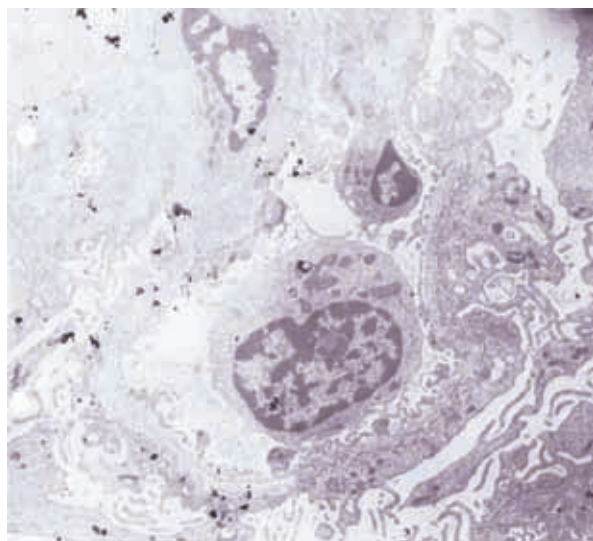


a. Periodic acid-Schiff staining – Magnification x20

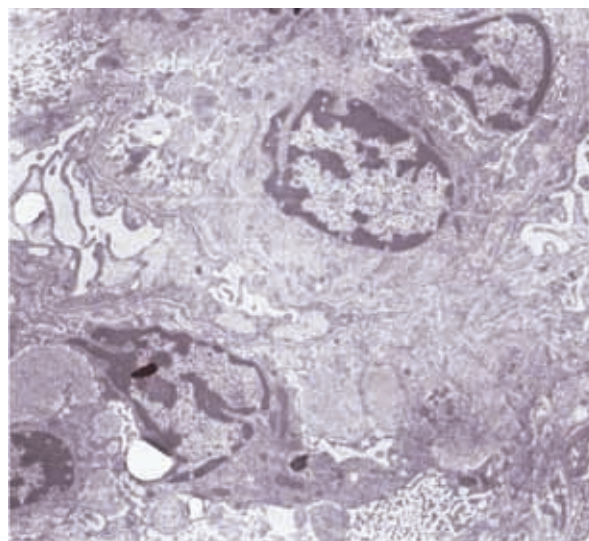


b. Trichrome staining – Magnification x20

Figure 3
Kidney biopsy (light microscopy).
Segmental necrosis and rupture of the GBM with cellular crescent formation.



a. Magnification x3600



b. Magnification x4600

Figure 4

Kidney biopsy (electron microscopy).

GBM showing thickening and splitting of the lamina densa (basket-weave appearance) and electron-lucent deposits.

DISCUSSION

The patient described in this report had positive family history for renal disease, with a classical clinical course of X-linked hereditary Alport syndrome.

Response to ciclosporin in Alport syndrome as a therapy for severe proteinuria is reported in the literature²¹. Nevertheless, it has also been described that prolonged ciclosporin use might be associated with reduced GFR and the rapid occurrence of ciclosporin nephrotoxicity²² and so some authors do not recommend its use in patients with Alport syndrome²². In fact, although ciclosporin therapy can decrease proteinuria in most patients with Alport syndrome, it may be associated with nephrotoxicity, precluding its long-term use^{22,23}. In this case, ciclosporin was stopped after four years to avoid or minimise its toxicity. It is also interesting to note that, as described by other authors¹⁸, progressive reduction/interruption of ciclosporin leads to deterioration of the renal function.

The histological spectrum of Alport syndrome is widely variable¹⁵. In this case, although it was not possible to perform immunostaining, renal biopsy

provided further information. Morphological changes of chronic ciclosporin toxicity (atrophic tubules, fibrosis) were not present, so ciclosporin nephrotoxicity was not suggested. Characteristic alterations of Alport syndrome were found on histological examination. The exception was the cellular crescent formation, involving a minority of glomeruli, which is not a usual finding in Alport syndrome.

Although rare, the evidence of crescentic proliferation in the pre-transplantation setting of Alport syndrome has been reported by some authors¹⁵⁻¹⁹. Nevertheless, it is still unclear if it is an accidental finding, as a super imposition of a morphological characteristic upon a pre-existing case of Alport syndrome, or a new morphological presentation of this syndrome, possibly associated to a more aggressive clinical course. The fact is that the number of glomeruli affected was reduced, less than 50%, with an apparent discrepancy between the number of crescents and the documented renal impairment. But it is also true that the renal specimen for biopsy only permits an estimate of the glomeruli involved. On the other hand, soon after the renal biopsy, serious renal function deterioration occurred and immunosuppressive therapy was

started as a rescue option. Transient response was noticed, but in the end renal function progressively declined. This fact may reinforce the idea of the crescent proliferation as a marker of unfavourable clinical outcome.

Despite negative ANCA serological test results, we are unable to entirely exclude the possibility of a superimposed pauci-immune necrotising and crescentic glomerular injury process. Some authors have speculated about the possible pathological mechanisms giving rise to the development of cellular crescent formation. Chang *et al.* suggested that the combination of the intrinsically high glomerular capillary blood pressure and the defective synthesis of collagen IV overwhelm the structural integrity of the GBM in patients with Alport syndrome¹⁵.

There are also references in the literature to a correlation between the clinical course of the disease and the severity of GBM alterations detected by electron microscopy¹³, so it is possible that the clinical evolution may be also related to the alterations identified by light microscopy.

CONCLUSION

This case draws attention to an uncommon pathological finding of Alport syndrome, the presence of cellular crescent formation. As it coincided with a rapid decline in renal function, it is difficult to identify its role as a cause or an epiphenomenon of the evolution observed. However, when found in a renal biopsy its presence can be interpreted as a marker of unfavourable outcome and therefore identify patients at a higher risk of rapid renal function deterioration.

Conflict of interest statement. None declared.

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