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Case report

Alport syndrome- a case report

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Abstract. The Alport syndrome is a hereditary, progressive form of glomerular disease that is often associated with neurosensorial hearing loss and ocular abnormalities. A mutation occurs in the genes encoding a protein from the type IV collagen family (α1-6 chains) which is the main component of the basement membrane and leads to a structural defect of the glomerular basement membrane. We present the clinical case of a 27-year-old woman, who came to our service with proteinuria and renal insufficiency discovered during pregnancy. The clinical and exploratory data led to the diagnosis of Alport syndrome and the therapy was conducted accordingly. Alport syndrome is a rare pathology in medical practice, which should be suspected since childhood, but starts to manifest mainly in young men and occasionally in women with hematuria, proteinuria, hearing loss and eye abnormalities.

Key Words: Alport syndrome, proteinuria, hematuria, renal insufficiency, hearing loss

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Introduction

Alport syndrome (also referred to as hereditary nephritis) is an inherited progressive form of glomerular disease that is often associated with neurosensorial hearing loss and ocular abnormalities (Kashtan et al 2018). It accounts for 0.6% of all patients who start renal replacement therapy in Europe and is most commonly transmitted as an X linked disorder with a gene frequency of 1 in 5000 (Flinter et al 1997). The Alport syndrome is caused by a defect in type IV collagen, a structural material expressed in many tissues, which is essential for the normal functioning of various parts of the body. These alpha chains of type IV collagen are normally found in different basement membranes within the kidney, cochlea and the eye. Abnormalities in these chains result in defective basement membranes at these levels, leading to the clinical features of this disorder (e.g., progressive glomerular disease, neural sensory hearing loss and ocular abnormalities) (Kashtan et al 2018). In about the 85% of cases, Alport's syndrome is X-linked and it involves mutations in the COL4A5 gene. In the remaining cases, it may be inherited in either an autosomal recessive, or rarely in an autosomal dominant manner; mostly, the condition is caused by mutations in the COL4A3 or COL4A4 genes. Coexisting mutations in COL4A3, COL4A4, COL4A5 or COL4A6 were found to cause an Alport's syndrome phenotype with digenic inheritance (Bruni et al 2019). In women, the disease is less severe compared to men. However, women with Alport's syndrome can have an accelerated form of their disease during pregnancy with worsening kidney function and they can also develop preeclampsia. Diagnosis of the condition is based on family history, clinical signs and specific procedures such as a kidney biopsy. The diagnosis can be confirmed by genetic testing. First described by Arthur C. Alport in 1927, over the years this syndrome became a pathology of high scientific interest. Currently, due to advances in diagnostic techniques, it is possible to make an early diagnosis postponing irreversible damages and avoiding life-threatening complications (Bruni et al 2019).

Case presentation

The 27-year-old patient was admitted to our service at 4 weeks after giving birth to a baby girl, for the assessment of an edematous syndrome developed during pregnancy which still persisted. She had a medical history of minimal proteinuria and hematuria for 3 years; there was no family history of kidney diseases. There was no previous chronic medication or other toxic use.
On clinical examination, she had important legs edema in the legs, bilateral deafness, normal blood pressure and urine output. Laboratory tests revealed a nephrotic syndrome with a 24 h proteinuria of 5.8 g, hypoproteinemia (5.2 g/dl) with hypoalbuminemia (3.1 g/dl). She associated moderate impairment of kidney function (with a creatinine of 3 mg/dl, urea of 135mg/dl), mild normochromic anemia and urine sediment with hematuria. We performed an etiological evaluation of the nephrotic syndrome. Autoimmune antibodies (antinuclear antibodies, anti-ds-DNA antibodies, p-ANCA, c-ANCA) were negative, screening for infections (ASLO, HCV, HBV, HIV) was negative. There were no clinical signs or lab tests suggestive of neoplasia.
The abdominal ultrasound revealed bilateral kidneys of normal size with preserved parenchymal index.
Considering the suspicion of an Alport syndrome, we continued the examinations with ENT, ophthalmological and renal biopsy examination. ENT examination detected bilateral neurosensorial hearing loss, without any infections in the ENT area. Ophthalmological evaluation detected the thinning of the temporal macular area.

Ultrasound-guided renal biopsy was performed after two months. The patient postponed it due to personal reasons. At the moment of the intervention, her evolution was good with decreasing renal lab values (creatinine of 1.3 mg/dl, urea of 80 mg/dl, proteinuria of 3 g/24h). She had received recommendations for adequate fluid intake and mild reduction of protein intake.
Light microscopy revealed 6 glomeruli with mild mesangial expansion (Fig.1), 1 glomerulus presented segmental sclerosis (Fig.2), mild focal tubular atrophy, reduced lymphocytic inflammatory infiltrate (Fig.3). Immunofluorescence was negative for IgG, IgA, IgM, C1q, C3, fibrinogen, kappa, and lambda light chains. In conclusion, the described morphological aspect correlated with immunofluorescence and clinical context strongly raised the suspicion of Alport syndrome.

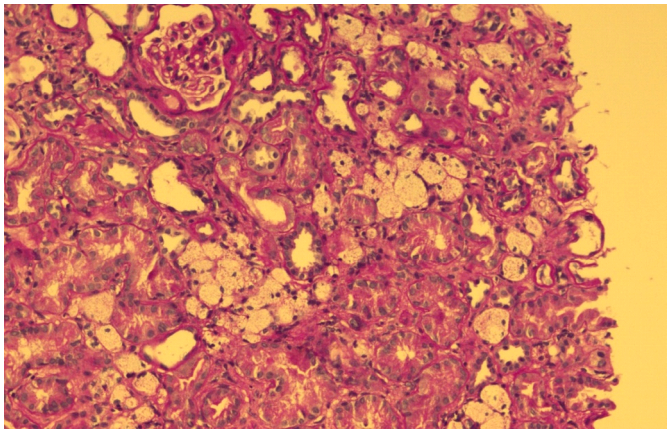

Fig. 1. Light microscopy: mild mesangial expansion (hematoxylin-eozin staining)

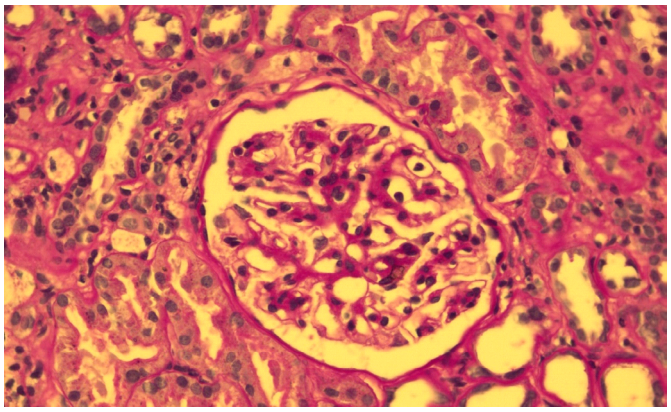

Fig. 2. Light microscopy: segmental sclerosis and mild mesangial expansion (hematoxylin-eozin staining)

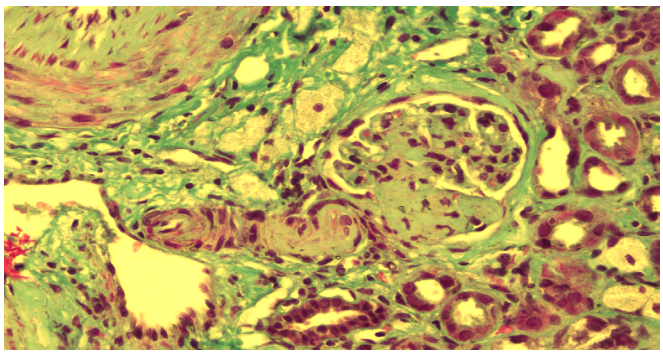

Fig. 3. Light microscopy: mild focal tubular atrophy, reduced lymphocytic inflammatory infiltrate and mesangial expansion (Masson trichrome staining).

Electron microscopy showed structural defect of glomerular basement membranes with thin, thick and split areas which sustain the diagnosis of Alport syndrome.
As a result, we interpreted the case as a chronic kidney disease due to Alport syndrome, associated with an acute kidney injury induced by the pregnancy status.
Regarding the lifestyle and diet recommendations, they included a moderate protein intake of about 0.8g/kg body weight /day, proper fluid intake, adequate nutrition, psychic hygiene, blood pressure control and treatment with oral iron supplements for anemia.
After two months, the patient showed a good recovery of the renal function (creatinine of 0.98mg / dl, urea of 46 mg/dl), serum albumin corrected to normal, mild hypoproteinemia (total protein of 6.1 g / dl), anemia was corrected, urinary examination with proteinuria decreasing to 2.9g/24h and mild remaining hematuria. After stabilizing the kidney function, we added to the previous recommendations an angiotensin-converting enzyme, ramipril, administered for antiproteinuric purposes with daily blood pressure monitoring and progressive titration to the maximum dose according to the blood pressure values, as well as monitoring of potassium levels.
We also started screening of the patients baby for Alport syndrome. Urine tests, renal function, ENT and ophthalmological exam were normal at the time of examination.
The particularities of our case were the following: the patient is a young woman, this syndrome being more common in men; our patient presented an acute kidney injury and worsening of the proteinuria during pregnancy and she had no family history of Alport syndrome.

Discussion

Individuals with Alport syndrome have a significant lifetime risk for kidney failure, as well as neurosensorial deafness and ocular abnormalities (Kashtan et al 2020). In severe cases, kidney failure occurs during adolescence or early adulthood, so most research has focused on remedies for kidney dysfunction (Omachi et al 2019). Autosomal dominant Alport syndrome is a disease with a low risk of ocular and hearing anomalies, but with a significant risk to develop renal failure although at an older age than the X-linked form (Marcocci et al 2009).
End-stage renal disease develops in most affected males, while affected females generally experience a benign renal disease (Bubalo et al 1991). Women with X-linked Alport syndrome should be tested at least annually for albuminuria and hypertension. The "Expert guidelines for the diagnosis and management of Alport syndrome" recommend treating patients presenting with albuminuria with renin-angiotensin-aldosterone system blockade (and adequate birth control because of the teratogenic risks of angiotensin converting enzyme inhibitors), because this will delay renal failure. Current recommendations consider that women with autosomal recessive Alport syndrome should be treated with renin-angiotensin-aldosterone system blockade from the time of diagnosis. In addition, women should be offered genetic counseling, informed about their reproductive options, and monitored closely during pregnancy for the development of hypertension and preeclampsia (Savige et al 2016).
Although no 'cure' currently exists, therapeutic blockade of the renin-angiotensin-aldosterone system can slow the progression

to end-stage kidney disease. Clinical trials for treatments in preventing chronic kidney disease have largely been negative over the last two decades, until recent trials have shown positive cardiovascular and renal outcomes of sodium-glucose co-transporter-2 (SGLT2) inhibitors (Mabillard et al 2020).
Treatment may include use of a hearing aid, hemodialysis and peritoneal dialysis to treat those with end-stage renal failure, with kidney transplantation as the last resort. Patients with Alport syndrome who undergo renal transplantation have generally excellent outcomes. Posttransplant antiglomerular basement membrane nephritis is a rare complication of renal transplantation for Alport syndrome. Because Alport syndrome is a genetic disorder, potential related donors must be carefully evaluated in order to minimize harm (Kashtan et al 2018).
Further studies are required to understand the exact pathophysiology of kidney damage that occurs in pregnant women with Alport's syndrome (Mehta et al 2013).

Conclusions

Alport syndrome is a rare inherited condition that occurs especially in young men with hematuria, proteinuria, hearing loss and eye abnormalities. Our patient represents a slightly special case, because she is a young female with Alport syndrome, which is a more uncommon case. Her kidney disease was discovered due to its worsening during late pregnancy. After giving birth, her renal function slowly improved, and proteinuria decreased; the Alport syndrome was diagnosed through kidney biopsy.

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