

X-linked Alport Syndrome: A Case Report

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Abstract

We report a case of an Alport syndrome. Etiology, clinical appearance, diagnosis, and treatment are discussed.

CASE REPORT

A 22-year-old African American male presented with a chief complaint of shortness of breath and chest pain. The patient states that he noticed that when he played basketball he tired with only minimal exertion. His exercise tolerance had been gradually decreasing over the past six months. The patient also complained of paroxysmal nocturnal dyspnea and new two-pillow orthopnea. The patient's chest pain was described as worse with inspiration and stabbing in nature.

The patient's past medical history included an episode of hematuria at age 12. The patient was evaluated with a renal biopsy which was determined to be inconclusive. On physical exam the patient was tachycardic with an elevated blood pressure of 205/148. Pulmonary exam revealed absent breath sounds at the bases and bilateral coarse crackles in the mid and lower lung fields. The rest of the physical exam was unremarkable.

Laboratories were pertinent for a BUN of 57 and creatinine of 5.8. A urinalysis revealed 500 mgs of protein. A chest x-ray revealed bilateral pleural effusions and hazy, patchy opacifications in the mid and lower lung zones bilaterally consistent with pulmonary edema. In subsequent discussion with the patient's mother it was learned that the patient had 2 uncles who were diagnosed with Alport syndrome in their 20s and subsequently received kidney transplants. The renal service was consulted but declined to biopsy the patient given his strong family history and previous biopsy which had been inconclusive.

A 24-hour urine revealed 1800 mg of total protein and a creatinine clearance of 15 ml/min. A renal ultrasound revealed normal sized kidneys with increased echogenicity consistent with medical renal disease. The ophthalmology service was consulted and an eye exam revealed anterior

lenticonus and corneal lesions consistent with Alport syndrome. Hearing tests revealed high-pitched sensorineural hearing loss which is also consistent with Alport. Lastly, a punch biopsy of the skin was performed and revealed absence of alpha-5 collagen, providing strong evidence for the diagnosis of Alport syndrome. The patient's hypertension and volume overload were controlled with an ACE inhibitor and loop diuretic and he was placed on the renal transplant list.

DISCUSSION

Alport syndrome, or hereditary nephritis, is a rare, progressive form of glomerular disease that affects 1 in 50,000 live births. It is a primary basement membrane disorder arising from mutations in genes encoding several members of the type IV collagen protein family. The disease is genetically heterogeneous, existing in X-linked, autosomal recessive, and autosomal dominant forms. Eighty percent of the disease is X-linked, 15% autosomal recessive, and 5% autosomal dominant. The most common, X-linked form arises from mutations in COL4A5, the gene encoding the alpha-5 chain of type IV collagen.

The hypothesis is that an abnormality in this chain impairs the integrity of the basement membrane in the glomerulus, cochlea, and eye, leading to the clinical manifestations seen in Alport syndrome. Incubation of skin biopsy specimens with a monoclonal antibody directed against the alpha-5 chain shows complete absence of staining in 80% of males with X-linked Alport syndrome. Thus, even the presence of epidermal basement membrane staining for the alpha-5 chain does not completely exclude the diagnosis. The same staining percentages exist with renal basement membranes. The histologic changes seen in the kidney in Alport syndrome include early thinning of the basement membrane and late development of longitudinal splitting of the

glomerular basement membrane on electron microscopy, producing a laminated appearance.

The clinical manifestations include recurrent episodes of gross hematuria, especially in childhood, as in the case vignette. The initial renal manifestation is usually asymptomatic microhematuria. Early in the course the plasma creatinine and blood pressure are normal, but eventually hypertension, azotemia, and proteinuria develop. End-stage renal disease is usually seen in males between the ages of 16 and 35, but some families have more indolent disease and develop renal failure in their 40s or 50s.

Extrarenal manifestations most commonly include eye and ear changes. Sensorineural hearing loss can take place and initially involve the high tones but can eventually affect the ability to hear conversational speech. Indeed, one of the patient's uncles was completely deaf in his 40s. Eye changes include anterior lenticonus, white or yellow flecking of the perimacular region of the retina, and corneal lesions such as posterior polymorphous dystrophy and recurrent corneal erosions. The diagnosis of Alport syndrome is usually established via a careful family history which reveals renal disease and deafness. However, in 15% of cases there is no family history and the diagnosis is established via renal biopsy. Given its non-invasive nature, immunohistochemical analysis of skin biopsies using a monoclonal antibody against the alpha-5 chain is becoming a popular initial step in the diagnostic work-up. Subsequently, a diagnosis of Alport syndrome can be confirmed or excluded in the majority of cases by the performance of a renal biopsy with analysis of type IV collagen expression in the kidney.

Treatment for Alport syndrome includes ACE inhibitors, which have been used to treat hypertension as well as reduce proteinuria. Cyclosporine has also been used to halt disease progression in those patients with severe proteinuria. In those patients with end-stage renal disease, both dialysis and transplantation are options, however anti-glomerular basement membrane disease can develop in 3-4% of transplanted patients. This complication is treated with

plasmapheresis and cyclophosphamide, but usually leads to loss of the allograft.

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