Autosomal Dominant Alport Syndrome Presenting as Proteinuria at Marine Corps Physical Fitness Test: A Case Report and Review

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Abstract

A 19-year-old Caucasian male presented to Nephrology Clinic for evaluation of proteinuria. He denied any hearing or vision impairment. The patient reported significant family history for kidney problem in his father, paternal uncle, paternal aunts and his half brother who shared the same father. Physical examination disclosed a serum creatinine of 0.7 mg/dl, 24-hour urine protein of 2.4 g and serum albumin of 3.7 g/dl. Urinalysis demonstrated dysmorphic red blood cells. A renal biopsy revealed the diagnosis of Alport syndrome. From his paternal family history, the disease was transmitted by autosomal dominant inheritance. The diagnosis of autosomal dominant Alport syndrome was made. He was prescribed lisinopril 5 mg per day. Referrals with Ophthalmology and Audiology were performed with showed no evidences of extrarenal involvement. At follow-up, 3 months later, patient continued to do well with serum creatinine of 0.7 mg/dl and urine protein-to-creatinine ratio of 1.75.

Alport syndrome is most commonly transmitted in an X-linked manner (80% of cases). Autosomal dominant transmission is rare and only accounts for 5% of affected patients. Extrarenal manifestations include hearing loss and ocular defects. Although the presence of these defects should prompt a search for Alport syndrome, patients with autosomal dominant Alport syndrome may present without these manifestations.

Keywords: Autosomal dominant; Alport syndrome; Hematuria; Hereditary nephritis; Proteinuria

Abbreviation: ACEI: Angiotensin-Converting Enzyme Inhibitors; ANA: Anti Nuclear Antibody; ARB: Angiotensin II Receptor Blockers; C3: Complement 3; C4: Complement 4; ESRD: End Stage Renal Disease; GBM: Glomerular Basement Membrane

Introduction

Alport syndrome or hereditary nephritis is a rare genetic disorder of the glomerulus with an incidence of 1 in 50,000 live births [1]. The disease is caused by abnormalities in type IV collagen, a key component of the glomerular basement membrane (GBM). Hematuria is the initial renal presentation of the disease, and often presents in childhood. Common extrarenal manifestations include sensorineural hearing loss and lenticonus of the anterior lens capsule. Classic Alport syndrome is inherited in an X-linked pattern and is the most common form of Alport syndrome (80% of cases). Autosomal recessive variant accounts for approximately 15% of cases. Autosomal dominant transmission is rare and only accounts for 5% of affected patients [1]. We report a case of autosomal dominant Alport syndrome presenting as asymptomatic proteinuria without significant extrarenal manifestations.

Case Presentation

A 19-year-old Caucasian–American male presented to Nephrology Clinic for evaluation of proteinuria. He was in the process of undergoing a physical for the Marine Corps and was found to have proteinuria. His past medical history was significant for asymptomatic microscopic hematuria and bilateral hip pain from femoro-acetabular impingement syndrome for which he occasionally took ibuprofen. He denied any hearing or vision impairment.

The patient reported significant family history of kidney disease (Figure 1) in his father, paternal uncle and paternal aunts. His half brother who shared the same father also had “red blood cells in his urine”. However, none of them had needed hemodialysis or kidney transplantation yet. Physical examination revealed a blood pressure of 136/60 mmHg with no peripheral edema. Laboratory evaluation disclosed a serum creatinine of 0.7 mg/dl, 24-hour urine protein of 3.7 g/dl. Urinalysis demonstrated dysmorphic red blood cells. A renal biopsy revealed the diagnosis of Alport syndrome. From his paternal family history, the disease was transmitted by autosomal dominant inheritance. The diagnosis of autosomal dominant Alport syndrome was made. He was prescribed lisinopril 5 mg per day. Referrals with Ophthalmology and Audiology were performed with showed no evidences of extrarenal involvement. At follow-up, 3 months later, patient continued to do well with serum creatinine of 0.7 mg/dl and urine protein-to-creatinine ratio of 1.75.

Alport syndrome is most commonly transmitted in an X-linked manner (80% of cases). Autosomal dominant transmission is rare and only accounts for 5% of affected patients. Extrarenal manifestations include hearing loss and ocular defects. Although the presence of these defects should prompt a search for Alport syndrome, patients with autosomal dominant Alport syndrome may present without these manifestations.

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Laboratory testing showed no anemia (HGB 16.1 g/dL, HCT 44.8 %, MCV 85.0 fl, and MCH 30.6 pg), serum creatinine of 0.7 mg/dL, 24-hour urine protein of 2.4 g, serum albumin of 3.7 g/dl and HbA1C of 4.7 %. Microscopic urinalysis demonstrated dysmorphic red blood cells (75-100/HPF). No abnormalities were noted on kidney ultrasound. Serologic workup was negative for anti-nuclear antibody, hepatitis B surface antigen, hepatitis C antibody and HIV.

Based on the family history, the pattern of inheritance was consistent with autosomal dominant. The patient subsequently underwent a kidney biopsy. Microscopic examination showed intact cortical tubules and normocellular glomeruli (Figure 2). Immunofluorescence revealed no significant staining. Electron microscopy revealed segmental to global GBM lamellation and segmental GBM thinning (Figure 3), diagnostic of Alport syndrome.

The patient was prescribed lisinopril 5 mg per day to reduce proteinuria. Referrals to Ophthalmology and Audiology were performed with showed no evidence of extrarenal involvement. Three months later, patient’s serum creatinine was 0.7 mg/dL and urine protein-to-creatinine ratio was 1.75.

Discussion

Alport syndrome, first identified by Dr. Cecil A. Alport in 1927 [2], is due to abnormalities of type IV collagen, a key component of the GBM. Type IV collagen molecules are composed of three alpha chains that form triple-helical structures through specific interactions of C-terminal noncollagenous domains and are made up of heterotrimers composed of combinations of 6 possible alpha chains [3]. These 6 distinct type IV collagen chains are encoded by 6 different genes that are arranged in pairs on 3 different chromosomes: COL4A1 and COL4A2 are on chromosome 13; COL4A3 and COL4A4 are on chromosome 2; and COL4A5 and COL4A6 are on chromosome X. The mutation of COL4A5 gene causes the classic X-linked form of Alport syndrome (85% of cases). Autosomal recessive inheritance arises from genetic defects in either COL4A3 or COL4A4 genes. Rare cases of autosomal dominant Alport syndrome due to heterozygous mutation in COL4A3 or COL4A4 also occur [1-4].

Clinical features of Alport syndrome including hematuria, sensorineural hearing loss, ocular defects and progression to renal failure are often seen in early adulthood. Hematuria is the most common (all males and 95% of affected female) and earliest manifestation, although some proteinuria may also present as in our case vignette. End Stage Renal Disease (ESRD) usually occurs between the ages of 16 and 35 years in patients with X-linked or autosomal recessive disease. The clinical features of autosomal dominant Alport syndrome are similar to those of X-linked disease. However, deterioration of renal function tends to occur more slowly [5-7].

Bilateral sensorineural hearing loss typically does not occur until adulthood. In general, the rate of hearing loss is similar to the progression of renal insufficiency. Ocular defects occur in up to a third of patients. Anterior lenticonus is the most common eye defect and pathognomonic of the disease. However, patients with the autosomal dominant form usually have less ocular abnormalities [8]. Leiomyomas are found in 2 to 5 percent of patients and carriers of X-linked Alport syndrome and are typically not seen in autosomal patterns [9]. The patient in our case study presented with non-nephrotic range proteinuria and microscopic hematuria without any evidence of ocular or hearing defects, and renal insufficiency.

In a kidney biopsy specimen, light microscopy may show no significant abnormalities in early stages. Glomerulosclerosis, interstitial fibrosis and prominent foam cells are seen in later stages. Immunofluorescence may show non-trapping of IgM. The characteristic finding of longitudinal splitting of the lamina densa of the GBM detected by electron microscopy (Figure 2) is diagnostic of Alport syndrome. A less invasive potential method to diagnose a child with suspected X-linked Alport syndrome is a skin biopsy using monoclonal antibody against the alpha-5 type IV collagen chain; however, this test cannot detect autosomal inheritance forms which are caused by mutation in COL4A3 and COL4A4 genes [10].

Differential diagnosis of Alport syndrome includes other glomerular disorders that present in children with microscopic hematuria such as IgA nephropathy and thin basement membrane nephropathy. In IgA nephropathy, family history is usually negative. On the other hand, the family history may be positive for hematuria in thin basement membrane nephropathy, but renal failure and deafness are typically absent [11].

There is currently no specific treatment for Alport syndrome, although the use of angiotensin-converting enzyme inhibitors (ACEI), Angiotensin II Receptor Blockers (ARB) or cyclosporine [12] has been described in uncontrolled studies. A number of reports showed evidence of decreased proteinuria in response to ACEI [13-16]. In patients who develop ESRD, the preferred modality of renal replacement therapy is transplantation. Although approximately 3% of transplanted males develop de novo anti-GBM disease [17], there is currently no report of recurrent Alport syndrome in the transplanted individual. Although the patient in our case report was normotensive, he was prescribed an ACEI to reduce proteinuria. At follow-up, the patient continued to do well without progression of disease.

Conclusion

The clinical manifestations of autosomal dominant Alport syndrome are similar to those of X-linked inheritance. However, deterioration of kidney function tends to occur more slowly. Visual...
and hearing defects are characteristic features observed in patients with Alport syndrome, but do not occur in those with thin basement membrane disease, a relatively more common cause of asymptomatic hematuria. Although the presence of ocular or hearing defects should prompt a search for Alport syndrome, patients with autosomal dominant Alport syndrome can present without these manifestations and may hence prove harder to diagnose.

Consent

The patient provided written consent for the publication of this case report and any accompanying images. A copy of the written consent is available for review by the journal’s Editor-in-Chief.

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References