

Unusual Case of Post-Infection Nephritis Associated with Nephrin Mutation

Osama Y Safdar^{1*}, Badr Alaifan², Abdulellah M Alturkistany², Ghadeer Mokhtar³ and Sherif M Desoky¹

¹Pediatric Nephrology Unit, College of Medicine, King Abdulaziz University, Saudi Arabia

²College of Medicine, King Abdulaziz University, Saudi Arabia

³Pathology Department, College of Medicine, King Abdulaziz University, Saudi Arabia

Abstract

NPHS1 gene is the gene responsible for production of Nephrin, which has role in the structure of glomerular filtration barrier. Nephrin located in slit diaphragm, which has a role in preventing passage of plasma proteins out of glomerular capillaries.

Keywords: NPHS1 gene; Nephrin; Inflammation; Hematuria; Oliguria

Introduction

The NPHS1 gene is responsible for the production of nephrin, which plays a role in the structure of the glomerular filtration barrier [1]. Nephrin is located in the slit diaphragm, which prevents the passage of plasma proteins out of glomerular capillaries [1]. Thus, the decrease or malformation of nephrin will cause massive proteinuria without inflammation of the glomeruli in the biopsy [2]. Here, we present a case of NPHS1 mutation that presented as nephritic syndrome.

Case Presentation

A previously healthy 10-year-old boy with no history of previous edema was referred to our hospital with a history of acute onset of hypertension manifested by headache, blurring of vision, hematuria and oliguria, which was preceded by upper respiratory tract infection 2 weeks prior to hospital admission. He also developed an attack of tonic-clonic seizure as a manifestation of hypertensive encephalopathy. Urine dipstick showed protein +3. His blood pressure was 140/100 mmHg. Serum albumin was 32 (range 40.2-47.6) g/L, creatinine 123.76 (range 26.52-61.88) $\mu\text{mol/L}$, and eGFR 41.56 ml/min/1.73 m², sodium and other electrolytes were normal. Abdominal ultrasonography showed that the left kidney could not be seen, while the large right kidney was 12 × 5.4 cm, with increased cortical echogenicity and no ascites. Abdominal CT showed the single right kidney.

He was generally edematous with lower limb pitting edema up to the thigh, with positive shifting dullness due to moderate ascites. His blood pressure was 140/82 mmHg. Initial blood work showed a mildly elevated anti-streptolysin O titer of 293 (range, 0-200), low C3 of 0.19 (0.75-1.65) g/L and low C4 of 0.03 (0.2-0.6) g/L, with negative C-ANCA and P-ANCA.

On the first day of admission, we started him on IV pulse Methylprednisolone 600 mg/m², for 3 days; Furosemide 1 mg/kg twice daily, Atenolol 50 mg, once a day (OD); Amlodipine 10 mg, OD; Nifedipine 10 mg, OD; and Hydralazine 5 mg, Q4H. On the second day, Prazosin 1 mg, TID; and Spironolactone 50 mg, OD were added. His blood pressure began to improve on the fourth day of admission. Kidney biopsy was performed on day five (Figures 1-6). Six chemotherapy sessions were planned for him with Cyclophosphamide 500 mg/m² with a gradual increase to 1000 mg/m² as tolerated and treated him as a case of rapidly progressive glomerulonephritis. Upon discharge, the patient was vitally stable, afebrile, with blood pressure 115/79 mmHg, respiratory rate 30/minute, heart rate 90/minute, urine output 1 cc/kg/hour, and urine dipstick showing protein +3 and blood +4. Research-based mutation analysis of the genomic DNA showed the following result for the gene NPHS1: (Nephrin, NM_004646.3) Gene Mutation Zygosity NPHS1 Exon 7 homozygous.

The resulting exon coverage from this assay is ~95%, and therefore our analysis does not exclude the slight possibility of a false negative result. The mutations found in this assay are additionally confirmed via Sanger sequencing. We stopped the immunosuppressive therapy after obtaining the results of the gene study and kept him on angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers and diuretics.

Discussion

We present a case of acute post-strep glomerulonephritis in a 10-year-old boy with a congenitally absent left kidney, continuing to show persistent nephrotic range proteinuria that was resistant to all immunosuppressive therapies. Genetic testing revealed homozygous mutation of the nephrin gene.

Glomerulonephritis is inflammation of the renal glomeruli, which can exhibit different clinical presentation and different histological

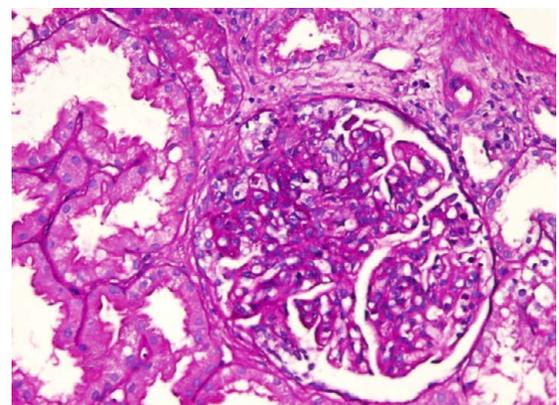


Figure 1: Preoperative T1-weighted coronal MR-image showing 1. Tumor with 4e ventricle obstruction; 2. Enlarged lateral ventricles with transependymal CSF egress.

*Corresponding author: Osamay Safdar, Pediatric Nephrology Unit, College of Medicine, King Abdulaziz University, Saudi Arabia, Tel: +966 800 116 9528; E-mail: safderosama@hotmail.com

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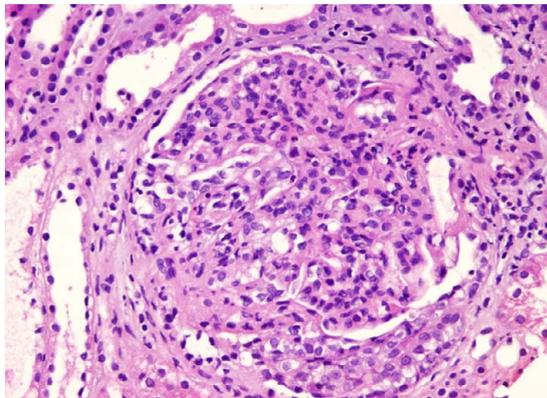


Figure 2: A glomerulus with moderate mesangial proliferation, segmental endocapillary proliferation and cellular crescent formation (H&E, 200X).

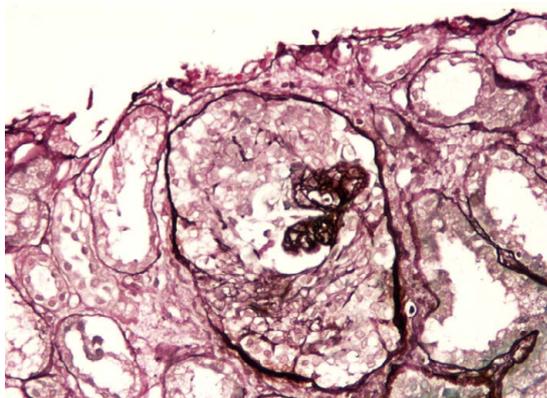


Figure 3: A glomerulus with circumferential fibrocellular crescents (JMS, 200X).

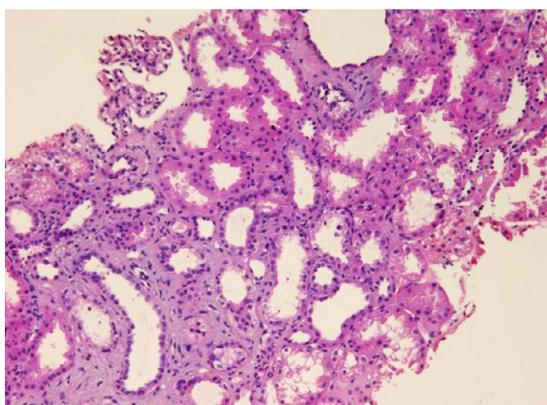


Figure 4: Mild focal interstitial fibrosis (H&E, 100X).

lesions [3]. The clinical presentation and responsiveness to treatment of glomerulonephritis can differ even in patients with the same histological lesion [3]. Poststreptococcal glomerulonephritis (PSGN) usually presents with gross hematuria, edema, hypertension and proteinuria [4,5]. It is estimated that 404,000 cases of PSGN occur annually in children younger than 15 years old, with approximately 97% in developed countries [6]. PSGN is usually preceded by upper respiratory

tract infection or impetigo and is usually resolved quickly, with a return to normal creatinine level in approximately 3 or 4 weeks [7].

The nephrin (NPHS1) gene is located in chromosome 19q13.1 with 29 exons and was identified by Kestilä et al. [8]. This gene is responsible for the production of a protein called nephrin, which is located at the slit diaphragm of the podocyte, suggesting that it plays an essential role in the filtration process [1]. Nephrin is a single-pass transmembrane protein consisting of eight extracellular Ig-like modules, a fibronectin type III-like motif, and a cytosolic C-terminal tail. Homodimers of nephrin and heterodimers with the glomerular protein NEPH1 constitute the structural basis of the slit diaphragm. NPHS1 gene mutation causes congenital nephrotic syndrome (CNS), which is most common in Finland with an incidence of 0.9 per 10,000.5 CNS patients presenting with severe nephrotic syndrome in the first 3 months of life, usually culminating in end stage renal disease [9,10]. However, recent studies showed that NPHS1 mutation could present as steroid-resistant nephrotic syndrome throughout the childhood age span [11,12]. Kari et al. in a retrospective study in King Abdul-Aziz University Hospital (KAUH) between 2002 and 2012, revealed that 2 out of 44 (4.5%) children older than one year of age who presented with steroid-resistant nephrotic syndrome had NPHS1 mutation [13]. Although nephrin mutation can present clinically in older age groups as steroid-resistant nephrotic syndrome, we did not find any cases that initially presented as nephritis. We believe that PSGN triggers the phenotype of the nephrin gene mutation.

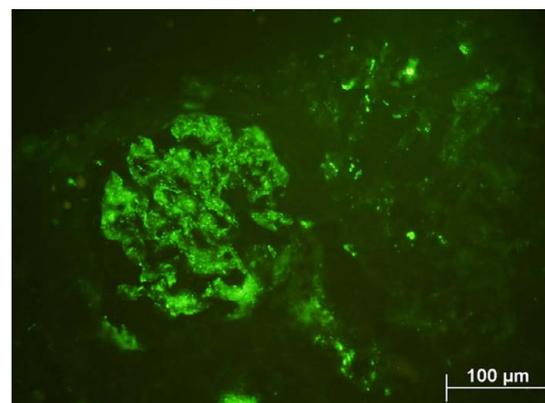


Figure 5: Strong positive granular staining of C3 along the capillary loops and mesangium (IF, 400X).

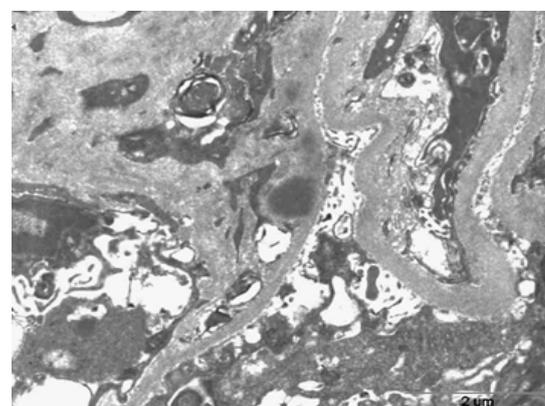


Figure 6: A subepithelial hump-like electron-dense deposit (TEM x 5752).

Conclusion

We believe that infection triggered an acute event and revealed a dormant disease, and after the acute event, the patient continued to have proteinuria related to a mutation in the slit diaphragm protein.

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