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Case Report

Enigmatic response of frequent use of rituximab in multidrug resistant nephrotic syndrome with focal segmental glomerulosclerosis with NPHS1 gene mutation children: genetic and pathophysiological consideration

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ABSTRACT

Childhood nephrotic syndrome due to focal segmental glomerulosclerosis (FSGS) usually refractory to multiple immunosuppressive drugs including rituximab. Nephrotic syndrome secondary to NPHS1 gene mutation also showed multidrug resistance with bad prognosis. Here, we are reporting a case who has multidrug resistant nephrotic syndrome with FSGS with NPHS1 gene mutation but responded well with frequent periodic use of rituximab.

Keywords: Multidrug resistant nephrotic syndrome, FSGS, NPHS1 gene mutation, Rituximab response

INTRODUCTION

Childhood steroid resistant nephrotic syndrome (SRNS) consisting 10% to 20% of childhood nephotic syndrome (NS).[1] Focal segmental glomerulosclerosis (FSGS) is the commonest histopathological lesions, minimal change disease (MCD) is the second most histopathological pattern and membranoproliferative glomerulonephritis (MPGN) following the MCD.[1] MCD and FSGS together are called as podocytopathies, in which disruption of slit diaphragm and normal podocyte function can lead to proteinuria and glomerular disease.[2] Histopathologically presence of segmental sclerotic lesions within glomeruli confirm the diagnosis of FSGS which causing NS.[3] Inspite of primary idiopathic FSGS, there are so many causes of FSGS including genetic and familial causes.Table-1 showing some genetic and familial cause of FSGS.[3] NPHS1 gene is responsible for nephrin protein synthesis which form the slit diaphragm. Mutation of this gene causing mainly Finnish type congenital nephrotic syndrome but non-familial sporadic form of childhood onset SRNS also happened. It causes massive proteinuria and rapid progression of end stage renal disease (ESRD) but sometime it has milder form of disease.[4,5] *In silico* scoring matrix evaluate the pathogenicity of amino-acid substitutions using the biophysical and biochemical difference between wild-type and mutant amino acid with the evolutionary conservation of the amino-acid residue in orthologs. This system observed both compound heterozygote and homozygote mutation of NPHS1 in familial and non-familial form of SRNS/FSGS. Disease would be mild to severe according to severity of amino acid substitution.[5] The management of SRNS remains a challenge for pediatric nephrologists, as there is no predictor for resistance to steroid therapy. Calcineurin inhibitors (cyclosporine and tacrolimus) are the main stay of treatment in non-genetic form of SRNS and their long-term prognosis is relatively good.[6] But genetic form of SRNS is unresponsive to immunosuppressive drugs as their non-immune mediated pathogenicity.[7] SRNS/FSGS has narrow therapeutic options once failed to respond to steroids and calcineurin inhibitors (CNI). Rituximab is a chimeric monoclonal antibody against the CD20 cell surface marker of B-cell and acts by depleting B-cells by causing apoptosis. It may also be helping by decreasing the interaction with regulatory T-cells, which help induce remission.[8] But it has been shown efficacious in various

studies to treat SSNS with varying results. However, there are limited data regarding its efficacy in SRNS.[9] We describe a case in which SRNS secondary to FSGS with NPHS1 gene mutation did not respond to multiple immunosuppressive drugs including CNI, but was successfully treated with 8-9 months interval use of rituximab in conjunction with CNI.

Table 1: Genetic and familial cause of FSGS.

Gene (protein effected)	Inheritance	Typical age of onset	Distinguishing clinical features
NPHS1 (nephrin)	AR	Infancy	Congenital nephrotic syndrome (Finnish type); severe nephrosis leading to ESRD
NPHS2 (podocin)	AR	3 months to 5 years	10-20% of SRNS in children
WT1 (Wilms tumor 1)	AD	Child	Diffuse messangial sclerosis/ FSGS±Wilms tumor or urogenital lesions
PLCe1 (phospholipase Ce1)	AR	4 months to 12 years	Diffuse mesangial sclerosis/FSGS
CD2AP (CD2-associated protein)	AR	<6 years	Rre, progresses to ESRD
INF2 (inverted formin 2)	AD	Teen/young adult	Mild nephrotic syndrome, but progressive CKD
ACTN4 (α-actinin 4)	AD	Any age	Mild nephrotic syndrome, may develop progressive CKD
TRPO6	AD	Adult (age 20-35 years)	Nephrotic, progressive CKD
tRNA gene	Mitochondrial DNA	Adult	May be associated deafness, diabetes, muscle problems, retinopathy (maternal inheritance)

CASE REPORT

An eleven and half-year-old boy, second issue of non-consanguineous marriage presented with the complaints of generalized body swelling and white precipitation of urine for 2 weeks, scanty micturition for 1 week, cough and cold for same duration. His first attack of nephrotic syndrome occurred at the age of 2 years with no atypical features on 2013 and treated with adequate dose and duration of oral prednisolone (6-6 weeks). That time he was responded within 2 weeks of oral prednisolone therapy. His first relapse was infection induced when he was on 22.5 mg alternate day prednisolone and it was 6 months after completion of treatment of 1st attack. Since then, he had multiple relapses and subsequently developed SRNS. He was treated with mycophenolate mofetil for 2 months, cyclosporin for one and half year, tacrolimous for one and half year along with high dose oral prednisolone. The child was given 1st courses (2 doses) of injection rituximab (RTX) at a dose of 375 mg/m^2/dose in 7-days interval on 29 October 2016 and 05 November 2016. Following RTX, the child remained asymptomatic for about 5 months. Subsequently he got 7 courses of RTX in home and abroad. He maintained remission on an average 10-11 months after each course of rituximab therapy. Renal biopsy was performed 2 times in home and abroad.

First renal biopsy was performed on 2014 and showed mild mesangial hypercellularity and a focus of mesangial sclerosis, immmunoflourescent (IF) study showed IgM and C3 in sclerotic tuft. Histological diagnosis consisted with FSGS. Second renal biopsy was performed on 2017 and showed focal mild increased in mesangial matrix, focal mild increased in mesangial cellularity, prominence of endocappilary cells and narrowing of capillary lumina, one glomerulous showed focal mesangial sclerosis with capsular synechiae, IF study showed focal taping of IgM and C3 in sclerotic tufts. They commented that mild mesangial hypercellularity and focus of mesangial sclerosis. Genetic study showed NPHS1 gene mutation. Finally, he was diagnosed as a case of FSGS with steroid toxicity with NPHS1 gene mutation.

On examination he was edematous, pallor absent, bed side urine for albumin was +++, ascitis was present. vitals were within normal limit (temperature-98 F, 82 beats/min, respiratory rate 30/min, blood pressure (BP)-120/80 mm of Hg), anthropometrically well thrived (height-148 cm, 50-75th percentile, weight-60 kg, 90th-95th centile, body mass index (BMI)-27.7 kg/m^2 >97th centile), and hypertrichosis was present.

Laboratory investigation showed hemoglobin 14.3 gm/dl, total count of white blood cell 13000/cmm of blood, neutrophil-65%, lymphocyte-31%, platelet count-450000/cmm of blood, urine routine and microscopic examination revealed +++ proteinuria, urine culture showed no growth, serum albumin-16 gm/l, urine protein creatine ratio was 4 mg/mg, serum creatinine-0.85 mg/dl, serum electrolytes-Na-134 mmol/l, K-4 mmol/l, Cl-100 mmol/l, TCO_2-22 mmol/l, blood urea-77.3 mmol/l, serum calcium-7.6 mg/dl, random blood sugar-4.2 mmol/l, LDL-32 mmol/l, HDL-393 mmol/l, triglyceride-312 mmol/l, ALT-37 U/l, serum thyroid level was 3.67 µIU/ml, serum T4 level was 7.8 ngm/dl, serum vitamin D level was 11 nmol/l, cyclosporine trough level 174 ngm/ml, serum immunoglobulin (IgG) level 9.6 gm/l, CD19 B-cell count was 1500/cumm of blood, percentage 35.75% of lymphocyte count and lymphocyte count was 4200/cumm of blood (by flow cytometry). This time he got 7th course

(one dose) of RTX along with tablet prednisolone in tapering dose, mycophenolate mofetil (SF-1/1/23), capsule cyclosporine 2.5 mg/kg/day (9/11/22) and antihypertensive drugs. Patient was on remission during discharge and subsequent follow up.

Table 2: Rituximab schedule.

Course	Date	Amount (mg/m^2)
1st		
Dose 1	29 October 2016	375
Dose 2	05 November 2016	375
2nd		
Dose 1	02 May 2017	375
Dose 2	09 May 2017	375
3rd		
Dose 1	05 September 2018	375
Dose 2	12 September 2018	375
4th		
Dose 1	02 April 2019	375
Dose 2	09 August 2019	375
5th		
Dose 1	10 August 2020	375
Dose 2	10 August 2020	375
6th		
Dose 1	05 March 2022	375
7th		
Dose 1	30 November 2022	375

Figure 1: 11 and half year-old boy.

DISCUSSION

Our patient had childhood SRNS with NPNS1 gene mutation and histopathologically FSGS. Patient was initially steroid responsive and subsequently developed multidrug resistant including steroid and CNI but responded well with rituximab.

With recent advancement of genetic study, along with congenital nephrotic syndrome NPHS1 mutations have also been identified in childhood-onset steroid-resistant nephrotic syndrome but disease course will be milder. Some sporadic and familial childhood-onset SRNS having compound heterozygous or homozygous NPHS1 mutations were identified. Their presentation was variable like severe to milder form due to amount of amino acid substitution.[5] Next-generation sequencing approaches identified approximately 30% of children with SRNS having causative pathogenic variants of mutation. Among these genes, NPHS1 and NPHS2 are more frequently identified.[11] Inefficient and potentially toxic immune-suppressive therapy should be avoided in SRNS patients with pathogenic variants of gene mutation. A small number of patients in this group having partial remission has been reported with calcineurin inhibitors and/or renin-angiotensin-aldosterone inhibitors. On the other hand, calcineurin inhibitors (cyclosporine and tacrolimus) constitute the current mainstay of treatment in non-genetic SRNS with around 70% achieving full or partial remission and an acceptable long-term prognosis. A better understanding of disease mechanisms may help identifying targeted therapeutic agents for patient with genetic mutation.[6,11]

Renal histopathology of our reported case also showed IgM and C3 deposition in sclerotic tuft. These findings described the prevailing hypothesis that immunological involvement of SRNS/FSGS and primary T-cell disorder that leads to glomerular podocyte dysfunction.[7,10] Experimental and clinical evidence suggests that immune mediated pathogenicity of SRNS/FSGS like our reported patient are responded well with immunosuppressive drugs than non-immune pathogenicity.[7]

CONCLUSION

In this case report, our clinical observation is insufficient to elucidate the exact mechanism of this enigmatic response of frequent periodic use of rituximab in multidrug resistant nephrotic syndrome due to FSGS with NPHS1 gene mutation. But immunological cause may be involved as well which was the reason for good response of rituximab.

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