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Steroid Resistance Nephrotic Syndrome

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Abstract

A 51 years old was diagnosis with nephrotic syndrome (NS) and treated with steroid and cyclosporine. He never achieve remission after 4 weeks of treatment. Histopathology lession shown a focal segmental glomerulosclerosis (FSGS). His kidney function was decreasing and eventually required hemodialysis. He was screened for hepatitis B, and HBsAg was reactive. We assume that the NS was secondary due to hepatitis B infection or in term hepatitis B virus associated nephropathy (HBVAN). Steroid resistance nephrotic syndrome (SRNS) mostly cause by FSGS. Focal segmental glomerulosclerosis is cause by podocytopathy. Genetic mutation cause alteration in gene coding for podocin. Treatment of SRNS include calcineurin inhibitor with or without low dose steroid. Evaluation of treatment done by 6 months to see if there is a minimum partial remission.

Keywords: SRNS; FSGS; Hepatitis B associated nephropathy; Glomerulonephritis; Hyperlipidemia; kidney; Hypoalbuminemia

Abbreviations: FSGS: Focal Segmental Glomerulosclerosis; ESRD: End Stage Renal Disease; SRNS: Steroid Resistance Nephrotic Syndrome; MCD: Minimal Change Disease; PCR: Polymerase Chain Reaction; NS: Nephrotic Syndrome; MMF: Mycophenolate Mofetil

Introduction

Nephrotic syndrome (NS) is manifestation of a glomerulonephritis characterized by massive proteinuria, hypoalbuminemia, edema and hyperlipidemia. Nephrotic syndrome can be a primary (idiopathic) and secondary due to other disease [1-3]. Increasing glomerular permeability to a large molecules such albumin and others protein is a hallmark of NS. Hypoalbuminemia is a consequence of massive proteinuria and lead to edema formation. Clinical course of NS is related to its histopathological variants and responsiveness to the corticosteroid [4].

Generally nephrotic syndrome response to steroid, but 10-20 % resistant to steroid and lead to end stage renal disease (ESRD) [5]. Focal segmental glomerulosclerosis (FSGS) is a histopathologic variant responsible for most steroid resistance nephrotic syndrome (SRNS) cases. Kidney biopsy showed that 12, 2-18, 7% is FSGS in adults [6]. Among those populations 8-28 % FSGS became steroid resistant. In childhood NS, minimal change disease (MCD) responsible for 20-25 % SRNS [5]. In United States about 4 % of FSGS progress to ESRD [7]. Persistent NS will worsen kidney progressively, increase risk of thromboemboli, hypertension, persistent hyperlipidemia, severe infection and low quality of life. Eventually o SRNS will progress to ESRD and required renal replacement

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therapy. We report a case of SRNS secondary due to hepatitis B.

Case Illustration

A 51 years old man, came to the hospital due to swollen of his whole body. He also felt dyspnea, distended abdomen and low of appetite. These conditions already happened for 1 year. He also has hypertension, high cholesterol serum, high uric acid and low albumin. He undergo a kidney biopsy, histopathology lession shown a focal segmental glomerulosclerosis. The urine analysis showed proteinuria (+3) with initial quantitative protein urine 13, 62 gr over 24 hours. He was then treated with methylprednisolone 16 mg once daily and cyclosporine 100 mg twice daily. The edema only resolves for 3 months, the methylprednisolone then decreased to 8 mg once daily and cyclosporine became 75 mg twice daily.

The quantitative protein urine was never as low as <3 gr/24 hours. The creatinine was increasing progressively from 2, 5 mg/dl to 7, 6 mg/dl within 6 months and the ultrasound shown a chronic parenchymal kidney disease. This patient had no olygouria and well responsed to diuretic. He was diagnosed with end stage renal disease and undergo a hemodialysis. He was positive for HBsAg, and did not know about hepatitis before. He has denied the disease of hepatitis, never had a blood transfusion previously, no heart disease, no kidney infection and was not an alcoholic.

The physical examination revealed general edema, normal vital sign, edema in both palpebral, increase jugular venous pressure, rhales in bilateral lung, normal heart function, there was ascites, and edema in both extremities. There was no sign of chronic liver disease. Laboratory showed low albumin 2,4 gr/dl, globulin 3,2 gr/dl, cholesterol 261 mg/dl, triglyseride 430 mg/dl, high density lipoprotein 23 mg/dl, low density lipoprotein 185 mg/dl, uric acid 10,4 mg/dl, ureum 230 mg/dl and creatinine 7,6 mg/dl. Rapid test for HIV and anti-HCV was negative. Urine analysis showed proteinuria (+3) with quantitative urine 13, 62 gr/24 hours. Chest x-ray showed normal lung and heart. Kidney biopsy showed a focal segmental glomerulosclerosis histopathology.

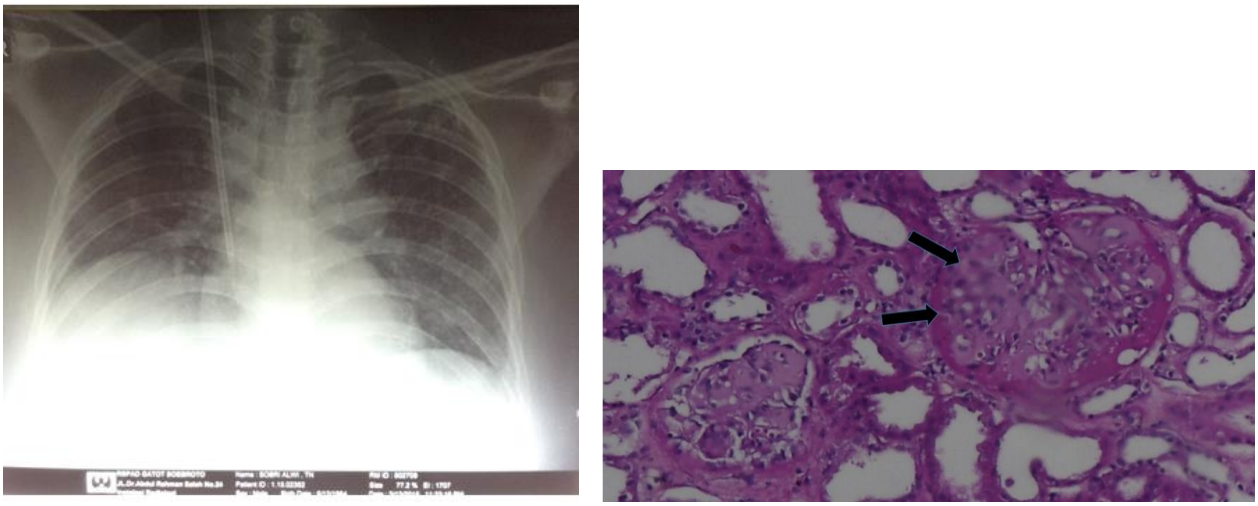

Figure 1: Histopathology lesion of glomerular.

Discussion

Nephrotic syndrome is one of kidney disorders characterized by proteinuria > 3, 5 gr/24 hours or > 300 mg/dl or (+3) in urine dipstick, hypoalbuminemia, general edema and hyperlipidemia [1,2,5,8]. In this case, the patient had quantitative protein urine 13, 62 gr/24 hours with low albumin serum 2,4 gr/dl, general edema and hyperlipidemia (cholesterol 261 mg/dl, triglyseride 430 mg/dl and LDL 185 mg/dl. These clinical appearances matched with a nephrotic syndrome.

Overall incidence of NS is 3 cases/100.000 a year [8]. Most of NS case is primary (idiopathic), in China, Zhou et al [9] found that 66 % of glomerular lesion in NS patient is due to primary and 33,4 % is caused by secondary disorders Carmen et al [10]. Found similar proportion of primary and secondary NS which is 56 % and 35 %

respectively. Nearly 90 % NS in childhood is due to primary disorder [11,12]. It seems that secondary causes of NS in adults has much more proportion than in childhood, this should be a consideration to seek secondary causes of NS before we initiate treatment for primary disorder.

Membranous nephropathy and FSGS contribute to one third case of primary NS in adults. Minimal change disease and IgA nephropathy were found in 25 % case of idiopathic NS. Among those lession, FSGS cause 3, 3 % new case of ESRD [13]. Among secondary cause of NS (Table 1), diabetes mellitus and systemic lupus erythematosus were the common cause of NS. Diabetes mellitus was found 10-25 % to cause NS, where lupus nephritis was found 16 % [8,9,13-18]. In histopathologic analysis by Zhou et al, hepatitis B virus infection cause glomerular lession which was found about 10,5 %.

Secondary causes of nephrotic syndrome	
Systemic disease	**Infection**
Diabetes mellitus	HIV
Systemic lupus erythematosus	Hepatitis B dan C
Amyloidosis	Mycoplasma
Malignancy	Syphilis
Myeloma	Malaria
Lymphoma	Schistosomiasis
Drugs	Filariasis
Gold	Toxoplasmosis
Antimicrobial	Congenital disorders
Non-steroid anti-inflammatory drug	Sindrom Alport syndrome
Penicilamin	Congenital NS Finnish type
Captopril	Pierson syndrome
Tamoxifen	Nail-Patella syndrome
Lithium	Denys-Drash syndrome

Table 1: Secondary causes of nephrotic syndrome.

Hull RP, Goldsmith DJ common forms of glomerular histopathologic lession in hepatitis B infection are IgA nephropathy, mesangial proliferative glomerulonephritis, minimal change disease and membranous glomerulonephritis [8, 19 20]. Hepatitis B infection rarely manifest as focal segmental glomerulosclerosis, but Kentaro, Sakallioglu et al. [21,22] report a case of FSGS as complication of hepatitis B infection and recovered after anti-viral was given. Clinical manifestations of hepatitis B associated nephroptathy (HBVAN) in adults are proteinuria and nephrotic syndrome (Table 2).

Characteristic of hepatitis B virus associated nephropathy (HBVAN)
Overt manifestations of nephrotic syndrome (proteinuria, general edema, hyperlipidemia dan hypoalbuminemia)
Hypertension
Progresive renal failure
Signs of chronic liver disease and abnormal liver function test

Table 2: Clinical characteristic of HBVAN [19,20].

Other manifestations such hypertention, decrease renal function and signs of chronic liver disease also typical in adult HBVAN. Massive proteinuria in HBVAN is a predictor of end stage renal disease requiring renal replacement therapy [19]. This patient had hepatitis B with nephrotic syndrome, proteinuria, hypertension and chronic liver disease in sonographic feature. These clinical appearance fit to a HBVAN complicated with ESRD. The kidney biopsy showed FSGS which is rare, but possible if we confirm a specific antigen or genome of HBV in glomerulus tissue by immunohistochemical or with a polymerase chain reaction (PCR) [23,24].

Generaly, management of secondary NS is to treat the underlying disorders. This patient had NS due to hepatitis B infection so that anti-viral is drug of choice Zhang, et al. [25]. Conducted a meta-analysis and suggest that antiviral decrease proteinuria, elimination of HBeAg and prevent progressive kidney failure. Corticosteroid in case of HBVAN increase risk of HBV reactivation and worsening liver and kidney function. This patient was in state of

compensated liver disease and it is not recommended to give steroid for this patient. Steroid is also avoided in case of viral replication is high and abnormal liver function tests [19,25].

We believe that if only HBV was detected earlier in this patient, the clinical course of nephrotic syndrome will be different. However, at admission this patient already was in an end stage renal disease and on hemodialysis program. Antiviral therapy may prevent further worsening of liver disease but not changing the prognosis of his kidney failure. There were no specified recommendation for antiviral therapy in HBVAN. Some antiviral may be effective such as: interferon alpha, lamivudine, famcyclovir, pegylated interferon, lobucavir and adepovir [20]. Recommended antiviral therapy for HBVAN based on metanalysis was interferon alpha and lamivudine, though lamivudine recently reported to be resistance to hepatitis B virus Lai ASH, Lai KN [25,19].

After steroid treatment for 4 weeks, remission will occure in most of NS cases and only small case respond more than 4 weeks [26]. However, 10-20 % case of NS in adult became steroid resistant [27]. Steroid resistant nephrotic syndrome based on KDIGO is defined as no remission after minimum exposure of prednisone 2 mg/kg/day or 60 mg/m^2/day for 4 weeks followed by 1, 5 mg/kg or 40 mg/m^2 per dose alternate-day for 4 weeks [1]. Other experts preferred defining SRNS as no remission after exposure of prenisone 2 mg/kg/day or 60 mg/m^2/day for 4 weeks [4,5,26,28].

In this case, patient received methylprednisone for more than 8 weeks with dose of 16 mg/day and then tapered to 8 mg/day and did not achieve improvement in proteinuria. We conclude this patient had a SRNS. Kidney histopathology shown a FSGS features. Reports mentioned about 80 % of FSGS is primary and the rest is due to secondary disorders [7,29,30]. There were only 20-25 % of FSGS achieve remission after steroid exposure and the rest became steroid resistant [31,32]. Focal segmental glomerulosclerosis contribute to most ESRD due to glomerular disease (In United States 4 % FSGS end up ESRD) [7]. Costicosteroid and immunosuppressive agents is first line drug of choice in primary FSGS. For cases of secondary FSGS, KDIGO found no proven efficacy of steroid use in those cases [1]. Focal segmental glomerulosclerosis is a heterogen disease. Terminology of FSGS is to describe primary lession in podocyte or known as podocytopathy which is frequently caused by circulating factors. This lession has 5 variants: not otherwise specified (NOS), collapsing, cellular, tip lession and perihiler variant. Collapsing form of FSGS has the poorer prognosis, low rate of remission and mostly resist steroid. While tip variant has the best prognosis related to high sensitivity of steroid and high rate of remission [33]. Genetic mutation coding podocyte is tought to be the main mechanism of developing FSGS. In FSGS there were absolute depletion of podocyte and changing its integrity. Podocyte is unable to support the fenestrated capillary in glomerulus followed by adhesion between glomerulus and bowman capsule. As consequences, glomerular filtration do not pass to bowman space but instestitial which cause segmental injury, interstitial fibrosis and tubular degeneration [34].

Genetic mutation that had been identified in podocytopathy are nephrin (NPHS1), podocin (NPHS2), alpha-actinin-4 (ACTN4), transient potential receptor cation, type 6 (TPRC6), CD-2 associated protein (CD2AP), wilm's tumor-1 (WT1), phospholipase c epsilon-1 (PLCE1/NPHS3), laminin-β2 (LAMβ2), inverted formin-2 (INF2), myosin heavy chain 9 (MYH9), dan apolipoprotein L1 (APOL1)[29,30,33,35,36,34-39]. Researches shown that mutation of NPHS2 and TPRC6 cause steroid resistance NS and progressive to be ESRD [35-36,38-41].

Principal management of NS is to manage hypertension, proteinuria, hyperlipidemia, edema, hypercoagulation and infection. Angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) is drug of choice for hypertension and reducing proteinuria. Blood pressure target below 125/75 in patient with proteinuria > 1 gr/24 hours is still controversy in case of NS. Adequate dietary protein should be ensured in the proteinuric patient (0,8-1,0 gr/kg daily) with a high carbohydrate intake to maximize utilization of that protein. Treatment of hyperlipidemia in patients with glomerular disease should usually follow the guidelines that apply to those at high risk for the development of cardiovascular disease. In high risk patient with cardiovascular event, statin is recommended. For edema, the mainstay of treatment is diuretics accompanied by moderate sodium restriction (1, 5-2 or 60-80 mmol sodium per 24 hours). Risk of thromboemboli is increase with albumin below 2, 5 gr/dl and immobilization. Prophylactic anticoagulant is recommended to prevent thomboemboli (eg. heparin 5000 unit subcutaneously every 12 hours). Infection in NS is potentialy lethal. Nephrotic patient is succeptible for infection of Pneumococcus. Early infection identification is vital to reduce mortality. Management of SRNS is somehow a chalange. First line drug for SRNS is calcineurin inhibitor (CNI) either cyclosporine or tacrolimus [1]. In case of partial remission by 6 months, the drug is continuing until 12 months followed by slow taper. If no remission by 6 months, discontinue CNI. Dose of cyclosporine range from 3-5 mg/kg/day divided into two doses, and tacrolimus is

0,1-0,2 mg/kg/day divided into two doses and titrate until serum tacrolimus achieve 5-10 ng/ml [1,42,43]. Low dose corticosteroid (30 mg/m^2 or 0,15 mg/kg/day prednisone) in combination with CNI is also recommended [1]. In this case, methylprednisolone was given 16 mg daily with combination of cyclosporine 100 mg twice daily. Our patient did not achieve even partial remission after 4 weeks of therapy. Other alternatives may be apply to this patient with steroid resistance are: mycophenolate mofetil (MMF), rituximab, cyclophosphamide, adalimumab, rosiglitazone, galactose dan adrenocorticotropin hormone (ACTH). However, only MMF, rituximab and cyclophosphamide reported beneficial for case of SRNS [1,28,42,44-47].Goals of treatment in NS is remission. Definition of complete remission is proteinuria below 0,3 gr/24 hours or urine protein to creatinine ratio < 300 mg/gr. While partial remission is proteinuria in range of 0,3 gr – 3,5 gr/24 hours or reduction of proteinuria at least 50 % from baseline and n below 3,5 gr/24 hours [1].

Conclusion

Nephrotic syndrome is one of glomerulonephritis manifestation which characterized by massive proteinuria, hypoalbuminemia, general edema and hyperlipidemia. In adults, incidence of secondary NS is higher than in childhood. Focal segmental glomerulosclerosis and MCD are the most histopathology variant found in secondary NS in adults. Nephrotic syndrome usually respond to steroid, but in small case they became resistant to steroid specially secondary NS. Management of secondary NS is to treat the underlying cause of NS. Kidney function worsen progressively and became ESRD.

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