

# Acute Kidney Injury in Primary Nephrotic Syndrome: Report of Nine Cases in Siriraj Hospital

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Acute kidney injury is a rare but important complication of nephrotic syndrome. We demonstrated here nine patients with nephrotic syndrome and oliguric renal failure in Siriraj Hospital during 2007-2009. Renal biopsy was done in every patient. The results were focal and segmental glomerulosclerosis (FSGS) in three patients, minimal change disease in four patients and collapsing focal segmental glomerulosclerosis in two patients. Seven patients had dramatic response to corticosteroid treatment within a few weeks and had rapid recovery of renal function. The exact mechanism of idiopathic renal failure is not well understood but it might be related to reduction in ultrafiltration coefficient of the glomeruli.

**Keywords:** Acute Kidney Injury, Renal Pathology, Nephrotic syndrome

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One of the important complications of the nephrotic syndrome that can be found occasionally is acute kidney injury (AKI). Many causes of AKI have been reported including severe intravascular volume depletion, acute tubular necrosis, acute interstitial nephritis<sup>(1,2)</sup>, bilateral renal vein thrombosis, rapid progression of original glomerular diseases, nephrotoxic drugs<sup>(3-5)</sup> etc. Some patients with AKI do not have any definite causes despite of meticulous history taking, physical examination and investigations. Chamberlain et al reported the condition of unexpected AKI with no definite cause in nephrotic syndrome in 1966<sup>(6)</sup>, but until now exact pathophysiology of this condition is still unclear. In Thailand, idiopathic AKI in nephrotic syndrome was seldom found and there were no previous reports in this topic. We collected nine cases of nephrotic syndrome that developed this complication and were treated in Siriraj Hospital. All of these cases had no other presumed causes of AKI,

such as, dehydration, nephrotoxic drugs, angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker. Objective of our report is to report pathology, natural history, response to treatment of this condition. Review literature including the prevalence, pathophysiology and therapeutic considerations were also shown.

## Case Report

### Case 1

A-47-year-old woman presented with generalized pitting edema for 2 months. She denied usage of other medications. At presentation she was edematous and her blood pressure was 130/80 mmHg. There was no clinical or laboratory evidence of hypovolemia or infection. Investigations revealed nephrotic syndrome with renal insufficiency (serum creatinine 1.4 mg/dl). Urinalysis showed massive proteinuria and no red blood cells. She was treated with prednisolone 1 mg/kg/d and furosemide 80 mg/d. After 2 weeks of treatment, she still was edematous and serum creatinine rose to 2.2 mg/dl; she was then admitted. Steroid was continued in same doses and human albumin infusion 20 g/d was also given. After 5 days of treatment, her serum creatinine decreased to

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1.2 mg/dl and renal biopsy was done.

Renal pathology revealed 13 glomeruli and was compatible with minimal change disease (MCD). Only mild tubular atrophy and interstitial fibrosis (20%) was also found with no characteristic of interstitial edema (Description of pathologies were described in Table 2). We continue treatment with prednisolone 1 mg/kg/d. When she came to follow-up 2 weeks after renal biopsy, she was less edematous and her serum creatinine decreased to 0.8 mg/dl. Now (about 50 weeks after first onset) her disease is in complete remission.

#### **Case 2**

A 52-year-old woman with biopsy proven focal segmental glomerulosclerosis (FSGS) for 6 months presented with massive generalized edema, ascites and oliguria for 2 weeks. In the past, she was treated with prednisolone 1 mg/kg/d and subsequently with oral cyclophosphamide 50 mg/day due to adverse effects of high dose steroid. Her disease was in partial remission (serum creatinine was 0.6 mg/dl and urine protein was 0.8 g/d) before she lost to follow-up for 1 month. At time of presentation she was massively edematous and had mild hypertension. There was no clinical and laboratory evidence of infection. Laboratory investigations confirmed relapse of nephrotic syndrome with AKI (serum creatinine 1.9 mg/dl). Urinalysis showed no significant RBC, WBC and casts. Prednisolone 1 mg/kg/d and oral cyclophosphamide 50 mg/d were restarted. After treatment for 6 days her serum creatinine gradually decreased to 1.5 mg/dl and then to 0.8 mg/dl on 9<sup>th</sup> day. On follow-up, 4 months after that episode, she is in partial remission and receives treatment with low dose prednisolone and oral cyclophosphamide (urine protein is 1.1 g/d).

#### **Case 3**

A 59-year-old woman with healthy condition presented with generalized pitting edema and foamy urine for 2 weeks. She also noticed oliguria for 1 week. At presentation she had massive edema, oliguria and severe hypertension. There was no evidence of hypovolemia or infection. Laboratory investigations found nephrotic syndrome with renal failure (serum creatinine was 3.0 mg/dl). Urinalysis revealed RBC 5-10/HPF with dysmorphic RBCs, WBC 3-5/HPF and no casts. She was treated with albumin infusion 20 g/d concurrent with intravenous furosemide. After treatment her serum creatinine gradually increased from 3.0 mg/dl to 5.7 mg/dl on 10<sup>th</sup> day after first presentation then renal biopsy was done for definite diagnosis. She

was still edematous despite of treatment with furosemide and her urine output was 400-600 ml/day.

The pathological result was compatible with focal segmental glomerulosclerosis. Mild hyalinosis of arterioles and mild intimal fibrosis of interlobular arteries were also presented. The patient was treated with prednisolone 1 mg/kg/d and discharged while serum creatinine was 5.5 mg/dl. On follow-up, 3 weeks after first onset, she had no edema, good urine flow and her serum creatinine decreased to 0.8 mg/dl. Now her disease is in partial remission (urine protein is 0.8 g/d).

#### **Case 4**

A 56-year-old woman with no underlying disease presented with progressive bilateral leg swelling for 4 weeks. She also developed oliguria for 4 days. At time of presentation, she was anasarca and normotension. She denied any medication or herbal usage and had no sign of infection. Laboratory findings revealed renal insufficiency (serum creatinine was 3.9 mg/dl), severe hypoalbuminemia and heavy proteinuria. She received treatment with albumin infusion for 1 week but there was no improvement in her renal function; prednisolone 1 mg/kg/d was then also started. Renal biopsy was done for definite diagnosis.

The pathological result showed minimal change disease with mild hyalinosis of arterioles and mild to moderate intimal fibrosis of interlobular arteries. After biopsy, treatment with steroid was continued. Her urine volume started to increase on 10<sup>th</sup> day after treatment. During follow-up, her serum creatinine normalized after first episode for 10 weeks (serum creatinine was 0.8 mg/dl). Now she is in partial remission state and receives treatment with low dose prednisolone.

#### **Case 5**

A 63-year-old man with well controlled-essential hypertension and psychosis for 5 years presented with progressive generalized edema, nocturia and foamy urine for 1 month. At presentation he had gross edema, oliguria and mild hypertension. There was no evidence of hypovolemia, infection or any drug abuse. Investigations revealed renal failure (BUN 62.7 mg/dl, serum creatinine 6.0 mg/dl) and heavy proteinuria. Urinalysis showed RBC 30-50/HPF with dysmorphic features, WBC 3-5/HPF and hyaline cast 5-10/LPF. Normal autoimmune profiles and complement levels. Ultrasound revealed normal size of both kidneys with mild increased echogenicity. With these features, rapidly progressive glomerulonephritis cannot be ruled

**Table 1.** Summary of baseline demographic and laboratory data of all nine patients

Patient No.	1	2	3	4	5	6	7	8	9
Age(year)	47	54	59	56	63	73	31	49	48
Sex	Female	Female	Female	Female	Male	Male	Male	Male	Female
Duration of NS	2 mo.	2 wks	2 wks	4 wks	1 mo.	1 mo.	3 wks	1 mo.	1 mo.
Blood pressure	130/80	148/93	186/96	122/79	150/100	175/87	107/70	150/90	140/90
Duration of AKI	22 days	9 days	20 days	76 days	22 days	14 days	10 days	35 days	24 days
Urine sediments (cells/HPF)	WBC 5-10, RBC 2-3	WBC 1-2, RBC 1-2	WBC 3-5, RBC 5-10	WBC 0-1, RBC 1-2	WBC 3-5, RBC 30-50	WBC 0-1, RBC 0-1	WBC 0-1, RBC 3-5	WBC 2-3, RBC 3-5	WBC 3-5, RBC 3-5
Proteinuria (g/d)	12.2	10.2	12.1	15.1	12.2	7.8	7.5	12.2	6.9
Initial serum BUN/Cr (mg/dl)	20/1.4	32/1.5	50/3.0	48/3.9	45/2.8	30/1.7	52/3.3	57/1.9	93/3.2
Peak serum BUN/Cr (mg/dl)	34/2.3	53/1.9	133/5.7	64/4.6	77/6.4	81.8/5.2	52/3.3	64/2.5	118.8/6.1
Serum Alb (g/dl)	1.8	1.5	1.8	2.0	1.8	1.8	1.1	1.6	1.8
Histopathology	MCD	FSGS	FSGS	FSGS	MCD, ATN	MCD	MCD	Collapsing FSGS	Collapsing FSGS, ATN
Treatment	Albumin iv 20 g/d x 6 d, Prednisolone 1 mg/kg/d	Albumin iv 20 g/d x 7d, Prednisolone 1 mg/kg/d	Prednisolone 1 mg/kg/d	Albumin iv 20 g/d x 7d, Prednisolone 1 mg/kg/d	Hemodialysis Methylpred → Pred oral 0.5 mg/kg/d	Albumin iv 25 g x 1 day, Prednisolone 1 mg/kg/d	Dexa iv 10 mg/d → Prednisolone 1 mg/kg/d	Albumin iv 20 g/d x 14d, Prednisolone 1 mg/kg/d	Prednisolone 1 mg/kg/d
Current status	CR	PR	CR	PR	CR	PR	PR	PR → death from infection	ESRD → death from infection
Current serum Cr (mg/dl)	0.8	0.5	0.8	0.9	1.0	1.2	1.0	-	-

Note : MCD = Minimal change disease, FSGS = focal and segmental glomerulosclerosis, ATN = acute tubular necrosis

**Table 2.** The pathological results of kidney biopsy of all nine patients

Case No.	Pathological Results
Case 1	LM: 13 glomeruli; 4 with global sclerosis (GS), none with segmental sclerosis (SS), normal appearance of other glomeruli. mild tubular atrophy and interstitial fibrosis (20%), mild interstitial mononuclear cell infiltrate (20%), no evidence of tubular necrosis, mild intimal fibrosis of interlobular arteries. IF: no staining for any immunoglobulins (Ig) and complements EM: 90% foot process effacement Dx – Minimal change disease
Case 2	LM: 10 glomeruli; 6 with SS, mild increased in mesangial cells and matrix, mild tubular atrophy and interstitial fibrosis (10%), no evidence of tubular necrosis, mild intimal fibrosis of interlobular arteries. IF and EM: not done Dx – Focal segmental glomerulosclerosis
Case 3	LM: 20 glomeruli, 2 with GS, 3 with SS, no crescents, other glomeruli showed only mild increased in mesangial cells and matrix, mild tubular atrophy and interstitial fibrosis (10%), no evidence of tubular necrosis, mild hyalinosis of arterioles and mild intimal fibrosis of interlobular arteries. IF: no Igs and complement staining. EM: 80% foot process effacement Dx – Focal segmental glomerulosclerosis
Case 4	LM: 6 glomeruli, no GS or SS, no crescents, mild increase in cells and matrix, moderate tubular atrophy and interstitial fibrosis (40%), mild hyalinosis of arterioles, mild to moderate intimal fibrosis of interlobular arteries. IF: no staining for all Igs, complements EM: 90% foot process effacement Dx – Minimal change disease
Case 5	LM: 11 glomeruli with mild segmental increased in mesangial cells and matrix, focal tubular injury and mild interstitial mononuclear cell infiltrate and edema, mild tubular atrophy and interstitial fibrosis (10%), unremarkable blood vessels. IF: no staining for all Igs and complements EM: 90% foot process effacement Dx – Minimal change disease, acute tubular necrosis
Case 6	LM: 5 glomeruli with normal appearance. No increase in mesangial cells and matrix. No sclerotic glomeruli and no crescents, mild tubular atrophy and interstitial fibrosis (20%), focal mild interstitial mononuclear cell infiltrate and edema, no evidence of tubular injury, unremarkable blood vessels. IF: no staining for all Igs, C3, C4 and fibrinogen. EM: 90% foot process effacement Dx – Minimal change disease
Case 7	LM: 22 glomeruli; none with sclerosis or crescents, none showed endocapillary proliferation, mild increase in mesangial cells and matrix, normal thickness of capillary walls, no tubular atrophy or interstitial fibrosis, no interstitial cell infiltration, no hyalinosis of arterioles, mild intimal fibrosis of interlobular arteries. IF: negative staining for all Igs, C3 and C4 EM: 80% foot process effacement of podocytes Dx – Minimal change disease
Case 8	LM: 8 glomeruli; 5 with segmental sclerosis, 2 of 5 glomeruli showed collapsing pattern with podocyte hyperplasia, no increase in mesangial cells and matrix, no thickening of capillary walls, no glomeruli with crescents or endocapillary proliferation, mild tubular atrophy and interstitial fibrosis (10%) and focal mild interstitial mononuclear cell infiltrate and edema, no abnormality in blood vessels. IF: no staining for all Igs, C3 and C4 EM: swollen endothelial cells and 100% foot process effacement Dx – Collapsing focal segmental glomerulosclerosis
Case 9	LM: 16 glomeruli; 3 with segmental sclerosis, 2 with collapsing lesion, no increase in mesangial cells and matrix, no crescents or endocapillary proliferation, diffuse tubular injury and mild interstitial edema, no tubular atrophy and interstitial fibrosis, mild intimal fibrosis of blood vessels. IF: no staining for all Igs, C3 and C4 EM: swollen endothelial cells and 100% foot process effacement Dx – Collapsing focal segmental glomerulosclerosis, acute tubular necrosis

Note: LM – Light microscopy, IF – Immunofluorescence, EM – Electron microscopy

out then we treated him with pulse methylprednisolone 500 mg/d for 3 days. Hemodialysis was initiated due to volume overload and preparation for kidney biopsy.

The renal pathological result was compatible with MCD. We also demonstrated mild interstitial mononuclear cell infiltrate, edema and features of acute

tubular necrosis. Prednisolone 30 mg/d was started after completed doses of MP. Five days after first dose of MP, significant diuresis was seen and serum creatinine decreased from 4.8 mg/dl to 3.9 mg/dl at 9<sup>th</sup> hospital day; then he was discharged. On follow-up, 3 weeks after biopsy, he had no edema, his serum creatinine

returned to 1.0 mg/dl and urinalysis revealed no RBC. Now he is in complete remission and his BP is well-controlled.

#### **Case 6**

A 73-year-old man with history of well-controlled essential hypertension for 10 years presented with mild swelling of both upper and lower extremities for 4 weeks. The patient also noticed oliguria for 4 days. He denied usage of any medication other than antihypertensive drugs that was used to control HT. He had no symptoms and signs of hypovolemia or infection. Laboratory findings revealed renal impairment (Serum creatinine 4 mg/dl), heavy proteinuria and severe hypoalbuminemia. Oral dexamethasone was started at dosage 5 mg/day. Human albumin 25 g was infused for 1 day but there was no response to treatment. Furosemide 80 mg/d intravenous was also prescribed. Increased amount of urine was seen in 3<sup>rd</sup> day after steroid treatment and serum creatinine began to decrease on 7<sup>th</sup> day.

The renal biopsy revealed MCD with mild tubular atrophy and interstitial fibrosis. We switched from dexamethasone to prednisolone 60 mg/d. Serum creatinine decreased to 1.2 mg/dl before discharge (after began steroid treatment for 2 weeks).

#### **Case 7**

A-31-year-old man with history of steroid responsive nephrotic syndrome 15 years ago presented with generalized pitting edema for 3 weeks. He was in healthy condition until this presentation. At time of this presentation, he was edematous, oliguria and normotension. Investigations showed acute kidney injury (serum creatinine was 3.3 mg/dl), severe hypoalbuminemia and heavy proteinuria. He was treated with prednisolone 1 mg/kg/d and underwent renal biopsy.

The pathology of kidney was compatible with MCD. The patient was treated with intravenous dexamethasone for 2 days and continued with prednisolone 1 mg/kg/d. On 3<sup>rd</sup> day after treatment, his urine volume began to increase and his serum creatinine gradually decreased to normal value within 10 days. Presently, he still receives prednisolone treatment.

#### **Case 8**

A-49-year-old healthy man presented with progressive severe edema for 1 month. He also developed oliguria for 4-5 days. He came to urban hospital that found he had anasarca, hypertension and

oliguria. Investigations revealed renal insufficiency (serum creatinine was 2.5 mg/dl), severe hypoalbuminemia and heavy proteinuria. HBsAg, Anti-HCV, Anti-HIV and autoimmune profiles were all negative. He was treated with albumin infusion 20 g/d for 14 days and intravenous furosemide 80-160 mg/d. He also received prednisolone 1 mg/kg/d. Despite this treatment, he still had oliguria and his serum creatinine increased; he was then referred to Siriraj Hospital for renal biopsy.

The renal pathology revealed evidence of collapsing FSGS. Treatment with high dose prednisolone was continued. 1 month after treatment, his serum creatinine decreased to 1.3 mg/dl. However, he developed duodenal ulcer perforation and, subsequently, severe hospital acquired bacterial pneumonia. He passed away at 3 months after first episode of nephrotic syndrome.

#### **Case 9**

A-48-year-old healthy woman presented with swelling of both legs for 1 month. She was edematous, oliguria and mild hypertensive. Laboratory findings showed renal failure (BUN 93.4 mg/dl, serum creatinine 3.2 mg/dl), severe hypoalbuminemia and massive proteinuria. Viral profiles include Anti-HIV and autoimmune profiles were all negative. She was treated with prednisolone 1 mg/kg/d and diuretics. Albumin infusion 20 g/d was also tried but there was no response to any of the treatments. Her renal function gradually deteriorated and hemodialysis was needed because of uremia.

The renal biopsy revealed characteristic features of collapsing FSGS with acute tubular necrosis. The disease did not response to any treatment (including those of steroid, cyclophosphamide or albumin infusion) and she subsequently developed repeated episode of severe bacterial pneumonia. She passed away from septic shock after the first episode after 3 months.

#### **Discussion**

Nine cases of AKI complicating primary nephrotic syndrome with various pathological diagnosis were reported. Two cases with collapsing FSGS had unfavorable outcome as both patients died from severe infection. Collapsing FSGS pathology can cause AKI and prognosis for this diagnosis is poor<sup>(7,8)</sup>. There was no definite etiology of renal failure in the other seven patients for which biopsy results were MCD in four patients and FSGS in three patients. All seven

patients did not have infection or nephrotoxic drugs use. As previous report<sup>(9)</sup>, acute kidney injury was mostly associated with minimal change pathology (85% of AKI in NS) but we found nearly half of our patients who developed AKI with FSGS pathology. In two patients with a diagnosis of MCD, the number of glomeruli from renal biopsy was less than 25 glomeruli therefore FSGS cannot be ruled out. However, these two diseases may share the same pathogenesis. The exact mechanism of idiopathic renal impairment is not well understood but it may be related to reduced ultrafiltration coefficient of the glomeruli<sup>(9,10)</sup>. We did not observe any evidence of severe interstitial edema and tubular cast obstruction in our patients.

Demographical data of our patients were quite resembled those of a previous reports<sup>(9)</sup>. Most of our patients were in middle to old age, developed severe edema, hypertension, massive proteinuria and severe hypoalbuminemia. We also revealed varying in time to development of renal failure and degree of severity of impaired renal function as in previous reports; one patient needed short term hemodialysis.

All seven patients with idiopathic AKI responded well to steroid treatment. The steroid regimen varied from prednisolone 0.5-1 mg/kg/d to pulse methyl-prednisolone for 3 days. Urine output started to increase on 3<sup>rd</sup>-7<sup>th</sup> day after treatment with the steroid. Renal function of three patients recovered with corticosteroid treatment alone. Human albumin was infused in four patients. In one patient, albumin infusion alone for 7 days failed to improve GFR but his urine output started to increase after steroid therapy for three days. Another three patients who received albumin also concomitantly treated with corticosteroid. Thus, from our observation, mainstay of treatment in patients with AKI in NS is high dose corticosteroid. Prognosis in this condition is good, even in patients who required dialysis.

#### ***Acute Kidney Injury in Nephrotic Syndrome: Review Literature***

AKI is not an uncommon complication of minimal change disease. Incidence of AKI in minimal change disease was reported in many retrospective reviews ranged from 15 to 61% of patients<sup>(11-16)</sup>. Recent retrospective review by Waldman et al that included 95 adult patients with minimal change disease revealed 17 patients (17.8%) presented with AKI and 24 patients (25%) eventually developed at least one episode of AKI during follow-up<sup>(17)</sup>. Patients with AKI tended to be older, hypertensive, severe edema, had lower serum

albumin and heavy proteinuria<sup>(9,14,16,18)</sup>. There was varying in time between onset of NS and AKI (ranged from 7 to 90 days). However incidence of AKI in these studies may be overestimated the true incidence in overall populations because of only cases complicating with AKI may be selected more for renal biopsy.

#### ***Renal Histopathology***

From the review by Smith and Hayslett<sup>(9)</sup>, the most common pathological finding is minimal change disease (85%), followed by focal glomerular sclerosis (8%). Abnormalities of tubulointerstitium were frequent and wide spread, ranging from focal simplification of proximal tubule to frank tubular necrosis with marked interstitial edema. 60% of patients were designated as acute tubular necrosis (ATN) while 40% had no tubular damage found. Presence of ATN was also associated with more severity of renal insufficiency.

Two reports also revealed abnormality in anatomic features of renal blood vessels<sup>(18,19)</sup>. Intimal fibrosis of arteries and hyalinosis of arterioles were more commonly found in patients with NS who developed AKI. Jennette and Falk also observed more prevalence of ATN histopathology in the patients with AKI<sup>(18)</sup>. These investigators suggested that ischemic ATN may be the principal abnormality present in most of these cases, but basis of injury is unknown. However these findings may be associated by chance in that arterial sclerosis is commensurate with the relatively advanced age in their patients.

#### ***Pathophysiology***

Exact pathophysiology of acute renal failure in nephrotic syndrome was still uncertain. The most likely factor underlying low GFR in nephrotic syndrome is reduced glomerular permeability due to functional changes of podocytes that lead to abnormality in ultrafiltration coefficient of glomerular basement membranes and the various mechanisms that can contribute to renal failure were described as follows:

##### ***Ineffective circulatory blood volume<sup>(9,20)</sup>***

The traditional view of pathogenesis of edema formation in NS held that the decrease in plasma oncotic pressure resulting from hypoalbuminemia would activate transudation of plasma fluid to interstitial space, resulting in hypovolemia<sup>(6)</sup>. Afterwards many reports demonstrated that blood volume in NS patients were normal or even slightly expanded<sup>(10)</sup>. No demonstrable difference exists between blood volume in nephrotic and normal individuals. In addition, renal blood flow in

minimal change nephrotic syndrome that estimated by p-aminohippurate (PAH) clearance technique appears to be normal or only slightly reduced<sup>(9)</sup>, cannot be explained renal failure. However, hypovolemia is still the important factor for develop renal failure in children with congenital NS that have persistent severe proteinuria enough to inability to maintain blood volume. Hypovolemia is also suspected in patient with overt hypotension or have obvious history and clinical features such as post-surgery and sepsis.

#### ***Ischemic acute tubular necrosis***<sup>(18,19,21)</sup>

In some cases, acute tubular necrosis was thought to supervene when renal ischemia was severe. Increased endothelin-1 expression in vessels, tubules, and glomeruli of patients with minimal change disease with acute renal failure may superimpose further vasoconstriction and hypoperfusion<sup>(21)</sup>.

#### ***Interstitial edema***<sup>(22,23)</sup>

Lowenstein et al proposed a theory of nephrosarcoma or severe interstitial edema of the kidney, which led to vascular or tubular occlusion, subsequently increased intratubular pressure then filtration failure was occurred<sup>(22)</sup>. In some patients, renal biopsy found severe interstitial edema but not in all cases. This hypothesis has been challenged by later studies that fail to improve renal function with aggressive fluid removal with dialysis or diuretics. We did not observe severe interstitial edema in our patients

#### ***Tubular obstruction***<sup>(24,25)</sup>

Stephens et al speculated that tubular cast formation as result of heavy proteinuria could obstruct luminal fluid flow, raise intratubular pressure, and thereby lower transcapillary pressure gradient<sup>(24)</sup>. However, minority of biopsy findings found cast formation. None of our patients' renal pathologies showed cast obstruction.

#### ***Reduced glomerular permeability***<sup>(9,10)</sup>

This hypothesis is vastly believed in the present. Primary reduction of ultrafiltration coefficient of glomeruli could impair GFR in nephrotic syndrome, either by a reduction in glomerular surface area available for filtration, by change in effective water permeability, or both<sup>(9)</sup>. Recent report from Vande Walle et al assessed 11 children with biopsy-proven minimal change disease and oliguric renal failure<sup>(10)</sup>. All patients had a significantly decreased GFR, whereas most renal plasma flow values were within normal range. GFR did

not improve with volume expansion with human albumin. This resulted in significant decreased filtration fraction, which was extremely low (<7%) in 4 patients. The results are consistent with principal role of reduced glomerular permeability due to foot process fusion.

In general, there may be many factors lead to development of acute renal failure in nephrotic syndrome in the patient. The principal factor underlying low GFR should be reduced glomerular permeability in minimal change disease, if occur extremely, may result in AKI. In other glomerular pathology, such as FSGS, the true pathophysiology of renal failure is still unclear.

#### ***Diagnosis and Treatment***

Careful history taking and physical examination should be done to rule out other precipitating causes of renal failure such as drugs, infection, hypovolemia before idiopathic acute kidney injury was diagnosed. Rapidly progressive glomerulonephritis or chronic kidney disease that associated with nephrotic syndrome should also be ruled out. Renal biopsy is still important for definitive diagnosis.

From literature reviewed, no single therapy or combination of factors emerged as predictors of a successful outcome<sup>(9)</sup>. However, corticosteroid was necessary for treatment of AKI in nephrotic syndrome. In other reports, steroid also was combined with other treatments such as diuretics, hemofiltration, etc. In our experience, every case of idiopathic renal failure responded well to corticosteroid alone. The regimen varied from prednisolone 0.5-1 mg/kg/d to pulse methylprednisolone. Urine output increased after treatment with steroid for 3-7 days. It was not surprising, because minimal change disease and some cases of FSGS respond well to steroid. We recommended corticosteroids treatment in every case of AKI in MCD or FSGS. Discontinuation of NSAIDs might result in improvement of renal function. Volume expansion with colloid or albumin was frequently given as an empiric treatment in nephrotic syndrome with AKI. However, the benefit of this treatment remains controversial. Stephen et al reported 3 nephrotic patients responded promptly to volume challenge with albumin infusion and mannitol<sup>(24)</sup>. In contrast, many reports failed to show improvement in renal function<sup>(10, 19)</sup>. Moreover, it may result in fluid overload and pulmonary edema<sup>(10)</sup>. Therefore volume expansion should be tried only in the case of significant hypovolemia. Diuretics treatment may also be useful in case presented with markedly edema. The nephrosarcoma

hypothesis has been debated by many subsequent reports. Therefore we do not recommend aggressive diuresis in this condition. Overdiuresis may cause further impairment in renal function. Temporary dialysis should be needed in some cases with severe AKI.

Almost all patients with this complication resolved after treatment as described above although short-term renal replacement therapy was required in some patients. Infrequently, a few patients with AKI may fail to recover, thereby requiring long term renal replacement therapy. Because of favorable outcomes and good response to treatment, we suggest to extensive workup and treatment for this condition.

### Conclusion

Acute kidney injury in nephrotic syndrome is rare but important. The cause of acute kidney injury per se can be managed with corticosteroids alone. Most cases began to recover within 1 week. Only mild interstitial edema was seen which might not explain renal failure. Minimal change disease and FSGS are the common pathologies of this condition.

### Potential conflicts of interest

None.

### References

1. Alper AB Jr, Meleg-Smith S, Krane NK. Nephrotic syndrome and interstitial nephritis associated with celecoxib. *Am J Kidney Dis* 2002; 40: 1086-90.
2. Revai T, Harnos G. Nephrotic syndrome and acute interstitial nephritis associated with the use of diclofenac. *Wien Klin Wochenschr* 1999; 111: 523-4.
3. Galesic K, Ljubanovic D, Bulimbasic S, Racic I. Minimal change disease and acute tubular necrosis caused by diclofenac. *Nephrology (Carlton)* 2008; 13: 87-8.
4. Grcevska L, Polenakovic M, Dzikova S, Grozdanovski R. Acute renal failure with severe tubulointerstitial changes in a patient with minimal change nephrotic syndrome treated with enalapril. *Clin Nephrol* 1997; 48: 331-4.
5. Olowu WA, Adenowo OA, Elusiyan JB. Reversible renal failure in hypertensive idiopathic nephrotics treated with captopril. *Saudi J Kidney Dis Transpl* 2006; 17: 216-21.
6. Chamberlain MJ, Pringle A, Wrong OM. Oliguric renal failure in the nephrotic syndrome. *Q J Med* 1966; 35: 215-35.
7. Albaqumi M, Soos TJ, Barisoni L, Nelson PJ. Collapsing glomerulopathy. *J Am Soc Nephrol* 2006; 17: 2854-63.
8. Albaqumi M, Barisoni L. Current views on collapsing glomerulopathy. *J Am Soc Nephrol* 2008; 19: 1276-81.
9. Smith JD, Hayslett JP. Reversible renal failure in the nephrotic syndrome. *Am J Kidney Dis* 1992; 19: 201-13.
10. Vande WJ, Mael R, Raes A, Vandekerckhove K, Donckerwolcke R. ARF in children with minimal change nephrotic syndrome may be related to functional changes of the glomerular basal membrane. *Am J Kidney Dis* 2004; 43: 399-404.
11. Primary nephrotic syndrome in children: clinical significance of histopathologic variants of minimal change and of diffuse mesangial hypercellularity. A Report of the International Study of Kidney Disease in Children. *Kidney Int* 1981; 20: 765-71.
12. Fujimoto S, Yamamoto Y, Hisanaga S, Morita S, Eto T, Tanaka K. Minimal change nephrotic syndrome in adults: response to corticosteroid therapy and frequency of relapse. *Am J Kidney Dis* 1991; 17: 687-92.
13. Huang JJ, Hsu SC, Chen FF, Sung JM, Tseng CC, Wang MC. Adult-onset minimal change disease among Taiwanese: clinical features, therapeutic response, and prognosis. *Am J Nephrol* 2001; 21: 28-34.
14. Korbet SM, Schwartz MM, Lewis EJ. Minimal-change glomerulopathy of adulthood. *Am J Nephrol* 1988; 8: 291-7.
15. Mak SK, Short CD, Mallick NP. Long-term outcome of adult-onset minimal-change nephropathy. *Nephrol Dial Transplant* 1996; 11: 2192-201.
16. Nolasco F, Cameron JS, Heywood EF, Hicks J, Ogg C, Williams DG. Adult-onset minimal change nephrotic syndrome: a long-term follow-up. *Kidney Int* 1986; 29: 1215-23.
17. Waldman M, Crew RJ, Valeri A, Busch J, Stokes B, Markowitz G, et al. Adult minimal-change disease: clinical characteristics, treatment, and outcomes. *Clin J Am Soc Nephrol* 2007; 2: 445-53.
18. Jennette JC, Falk RJ. Adult minimal change glomerulopathy with acute renal failure. *Am J Kidney Dis* 1990; 16: 432-7.
19. Esparza AR, Kahn SI, Garella S, Abuelo JG. Spectrum of acute renal failure in nephrotic syndrome with minimal (or minor) glomerular lesions. Role of hemodynamic factors. *Lab Invest* 1981; 45: 510-21.
20. Squire JR. The nephrotic syndrome. *Adv Intern*

- Med 1955; 7: 201-41.
21. Chen CL, Fang HC, Chou KJ, Lee JC, Lee PT, Chung HM, et al. Increased endothelin 1 expression in adult-onset minimal change nephropathy with acute renal failure. *Am J Kidney Dis* 2005; 45: 818-25.
  22. Lowenstein J, Schacht RG, Baldwin DS. Renal failure in minimal change nephrotic syndrome. *Am J Med* 1981; 70: 227-33.
  23. Cameron MA, Peri U, Rogers TE, Moe OW. Minimal change disease with acute renal failure: a case against the nephrosarcoma hypothesis. *Nephrol Dial Transplant* 2004; 19: 2642-6.
  24. Stephens VJ, Yates AP, Lechler RI, Baker LR. Reversible uraemia in normotensive nephrotic syndrome. *Br Med J* 1979; 2: 705-6.
  25. Venkataseshan VS, Faraggiana T, Grishman E, Marquet E, Churg J. Renal failure due to tubular obstruction by large protein casts in patients with massive proteinuria. *Clin Nephrol* 1993; 39: 321-6.

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**รายงานผู้ป่วยกลุ่มอาการเนโฟรติกที่มีภาวะไตวายเฉียบพลันแทรกซ้อน และทบทวนวรรณกรรมที่เกี่ยวข้อง**

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ภาวะไตวายเฉียบพลันเป็นภาวะแทรกซ้อนที่มีความสำคัญอย่างหนึ่งในผู้ป่วยกลุ่มอาการเนโฟรติกสาเหตุของภาวะไตวายเฉียบพลันในผู้ป่วยกลุ่มนี้บางรายไม่สามารถค้นพบชัดเจน คณะผู้นิพนธ์ได้รายงานผู้ป่วย 9 ราย ที่มีภาวะแทรกซ้อนนี้ซึ่งได้มารับการรักษาที่โรงพยาบาลศิริราชระหว่างปี พ.ศ. 2550-2552 ผู้ป่วยทุกรายไม่พบสาเหตุ ที่แน่นอนของภาวะไตวายเฉียบพลัน ทุกรายได้รับการตรวจชิ้นเนื้อไตทางพยาธิวิทยา โดยพบเป็นโรคไตชนิด *minimal change disease* 4 ราย, *focal and segmental glomerulosclerosis* 3 ราย และ *collapsing focal and segmental glomerulosclerosis* 2 ราย ผู้ป่วย 7 ราย ตอบสนองต่อการรักษาด้วยยาสเตียรอยด์ขนาดสูง ในเวลาไม่เกิน 1-2 สัปดาห์ แม้ว่าผู้ป่วย 1 ใน 7 ราย ก่อนเริ่มรักษาต้องได้รับการฟอกเลือดชั่วคราวหลังการรักษาการทำงานของไต สามารถฟื้นกลับมาได้จนปกติ กลไกของการเกิดโรคอาจจะเกี่ยวข้องกับการเปลี่ยนแปลงสัมประสิทธิ์การกรองของโกลเมอรูลัสในกลุ่มอาการเนโฟรติก การวินิจฉัยและการรักษาที่ถูกต้องจะช่วยให้การทำงานของไตกลับมาเป็นปกติได้

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