Case Report

Reversible Acute Renal Failure in a Young Man with Nephrotic Focal Segmental Glomerulosclerosis

Yung-Hsin Huang, Huang-Yang Tseng, Chih-Jen Wu, and Han-Hsiang Chen

Abstract

The nephrotic syndrome-associated acute renal failure is an infrequent but an alarming condition in patients with primary glomerular diseases. Pathophysiology is unclear and the following mechanisms are proposed to account for the acute decline in glomerular filtration rate (GFR): increased intrarrenal pressure secondary to interstitial edema, concomitant acute tubular injury, reduction of glomerular permeability, and noxious effect of heavy proteinuria on proximal tubular cells. We present a 26-year-old young man with nephrotic syndrome (NS) caused by focal segmental glomerulosclerosis (FSGS), complicated with an oliguric acute renal failure (ARF) requiring hemodialysis. Renal function did not improve in spite of fluid removal by hemodialysis. After prescribing steroid therapy, improvement of proteinuria and functional recovery of acute renal failure occurred simultaneously. Hence, this condition is well responsive to steroid therapy, which should be administered as early as possible for recovery of renal function.

KEY WORDS: nephrotic syndrome, acute renal failure, focal segmental glomerulosclerosis

Introduction

Acute renal failure (ARF) is a rare complication of adult idiopathic nephrotic syndrome (NS). In documented renal biopsy, minimal-change disease (MCD) is the most frequently seen etiology and the rest includes focal segmental glomerulosclerosis (FSGS) or mesangial lesions (1). In most patients, ARF develops early at the onset of first episode of NS, and recovers spontaneously or concurrently with steroid treatment. However, in a small number of cases, it may be severe enough to cause rapid decline in renal function accompanied by oliguria or anuria that is resistant to diuretic therapy thus necessitating renal replacement therapy, or may progress to end-stage renal disease (2). The exact pathogenesis for rapid decline in glomerular filtration rate (GFR) is not fully understood. Several mechanisms have been postulated such as increase in hydrostatic pressure in the tubule and Bowman’s space due to obstruction by protein cast (3) and/or interstitial edema (4); ischemic acute tubular injury secondary to transient hypovolemia and/or pre-existent arteriolosclerosis (5); reduction in ultrafiltration of glomerular basement membrane (6); and toxic injury to proximal tubular cells by heavy proteinuria (7). We report a case of reversible severe ARF requiring hemodialysis secondary to nephrotic FSGS.

Case Report

A 26-year-old man with a history of rheumatic heart disease status post mitral and aortic mechanical valve replacement, atrial fibrillation and hypertension...
Huang, Tseng, Wu and Chen presented to our branch hospital with edema of lower legs. Previous renal function was normal with creatinine (Cr) 0.9 miligram (mg)/deciliter (dL). Usual medications include coumadin, propranolol and oral furosemide 40 mg/day. His blood pressure was 123/88 mmHg, pulse rate was 83/min, and body mass index was 24.5. Laboratory data revealed blood urea nitrogen (BUN) 70 mg/dL, creatinine 2.6 mg/dL, albumin 2.5 gram/dL, total protein 6.9 g/dL, total cholesterol 293 mg/dL, triglycerides 92 mg/dL, and hemoglobin 9.8 g/liter. Urinalysis showed dipstick protein 3+, red blood cell 32/high-power field, negative cast and negative glucose. The spot urine protein to creatinine ratio (UPCR) was 6.12. Immunoglobulin (Ig)G, IgA, IgM, Complement (C)3 and C4 were within normal limits. Antinuclear factor, rheumatoid factor, cryoglobulin, classical - antineutrophil cytoplasmic antibody (C-ANCA), perinuclear - antineutrophil cytoplasmic antibody (P-ANCA), hepatitis B and C were negative. Kidney sonography revealed increased size of both kidneys and normal cortical echogenicity. Echocardiography reported as preserved global systolic function with ejection fraction of 62%. Renal function did not improve with diuretics, so hemodialysis (HD) was initiated on the 4th hospital day and maintained 3 times per week due to persistent azotemia and oliguria (Fig. 1). The patient initially refused renal biopsy, and worried about complications of steroid therapy due to his underlying heart problems. Severe proteinuria persisted (UPCR 10.6) till the 17th day and he finally accepted steroid therapy on the 25th day. Steroid pulse therapy with solumedrol 1 gram per day was administered for three successive days. Urine output increased thereafter, and we discontinued HD on the 28th day (Fig. 1). Then, oral prednisolone 0.5 milligram per kilogram body weight was prescribed, and renal function recovered to normal gradually. Moreover, protein excretion reduced to

Fig. 1. The serial alterations of serum BUN, serum Cr and urine amount per day are shown in relation to days of clinical course. The time period under the dotted square area represents regular hemodialysis period.
non-nephrotic range (UPCR 2.0) on the 40th day. After about 8 weeks of steroid therapy with the same dosage of medication, his UPCR remained 1.2, so we performed renal biopsy on the 90th day at our main hospital. The specimen contained a total of 20 glomeruli. Light microscopy showed some glomeruli with segmental sclerosis, renal tubules with thickened basement membrane, but unremarkable interstitium (Fig. 2). There were no staining for immunoglobulins or complement under immunofluorescence microscopy. Electron microscopy revealed effacement of foot processes of podocytes, but no electron-dense deposits. The pathological diagnosis was FSGS. We continued the same dosage of oral steroid therapy and UPCR dropped to 0.7 after about 5 months of therapy.

### Discussion

In clinical practice, NS-associated ARF is mostly seen in MCD. Other NS predominant glomerulonephritis conditions like FSGS may develop ARF, but is less common than MCD. Pure membranous glomerulopathy causing ARF is very rare. Only when superimposed with crescentic glomerulonephritis will membranous glomerulopathy present with ARF, active urinary sediments and cellular casts in urine (8). Aggressive glomerulonephritis such as rapidly progressive glomerulonephritis usually accompanies with ARF but with a different mechanism known as crescent formation. There were some reports about patients with NS concurrently using nonsteroidal anti-inflammatory drugs (9), or selective COX-2 inhibitors (10), or traditional medicine (11), or exposure to iodinated contrast medium (12), who develop ARF mostly secondary to drug/toxin-related acute or chronic tubulo-interstitial nephropathy. Our patient did not have exposure to these medications or conditions and did not use ACEI/ARB in the past and during hospitalization. He presented with NS-associated ARF and severe reduction of renal function at the onset of symptoms that required hemodialysis for about 4 weeks. This is a challenge for clinicians since the diagnosis of MCD or FSGS is unexpected initially unless a renal biopsy is performed early in the course of the disease.

The underlying pathogenesis of this serious complication remains uncertain. Early reports advocated the role of tubular obstruction by proteinaceous casts causing renal dysfunction, in which most cases are irreversible (3). This is unlikely in our patient as he attains recovery of renal function. Lowestein et al. suggested interstitial edema, also known as nephrosarca, as a key factor inducing ARF (4), but some authors disagreed with this hypothesis since minimal or no interstitial edema was noted in renal biopsy of their cases (6, 7). Owing to our patient’s personal considerations, renal biopsy had been unintentionally delayed till the 90th day of the disease course. Therefore, the histopathology might not reveal any superimposed interstitial edema or acute tubular injury at that time even if it initially coexisted. In view of persisting severe ARF despite fluid removal by hemodialysis for about 4 weeks, interstitial edema is surely not a predisposing factor in our patient, but it may coexist with other causes. Previous report claimed spontaneous or diuretic-induced hypovolemia as a precipitating factor (3). It is also less likely in our patient as he has no systemic hypotension or hypovolemic symptoms and the dose of furosemide is only 40 mg per
day. However, intrarenal ischemic tubular injury due to vasoactive factors triggered by preceding reduced effective blood volume before onset of ARF cannot be excluded in our patient. Some authors suggested that changes in glomerular permeability may play a major role in ARF occurring in NS (13). They hypothesized that decrease in GFR is determined by reduction in hydraulic permeability of the glomerular capillary wall, termed the ultrafiltration coefficient, which is in turn related to the extensive foot process effacement of podocytes (14). The mechanism of acute reduction in glomerular permeability alone could not explain well this severe form of ARF in our patient.

Furthermore, Stellato et al. proposed that toxic injury to proximal tubular cells by severe proteinuria may be the most important mechanism of ARF occurring in adult idiopathic NS patients (7). They found much protein droplets within the cells of proximal tubules due to uptake of filtered proteins including albumin and complement system components. This toxic injury is attributed to upregulation of inflammatory, vasoactive and fibrogenic genes, activation of complement cascade, and induction of apoptosis (14). Moreover, in the literature, high risk of ARF is found in idiopathic NS patients, who are male (15), old-aged (2, 15), with a higher blood pressure (2), more marked proteinuria (2) and severe hypoalbuminemia (2, 15). Although our patient is young and has blood pressure well under control, the extent of proteinuria is high, making it a key factor in inducing severe reduction in GFR during NS through the mechanism of toxic injury to tubular cell by this huge protein overload. Steroid therapy may reduce the exposure of tubular cells to toxic effect of heavy proteinuria (7). In our patient, improvement of proteinuria after steroid therapy also paralleled with the functional recovery of renal function. The detailed mechanism of steroid effect on GFR in ARF secondary to NS remains unknown, but it may allow the complete recovery of glomerular filtration fraction as proteinuria decreases (16). Meanwhile, the appropriate diuretic therapy or renal replacement therapy should be initiated and maintained for removal of excess fluid causing interstitial edema, in order to avoid a misbalance of pressures within the glomeruli and the subsequent progression to anuria.

Patients with primary FSGS may present with any level of proteinuria, nevertheless, the concern is greatest for those who present with nephrotic-range proteinuria and renal dysfunction because without appropriate treatment, they often follow an alarming progressive course to end-stage renal disease over three to six years (17). The rate of spontaneous complete remission among patients with NS-related FSGS is very low, probably less than 10 percent (18). Spontaneous remission is more likely to occur among patients with normal kidney function and non-nephrotic proteinuria (18). Although optimal dose and duration of steroid therapy are unknown, better results are obtained with an aggressive longer course of therapy rather than conventional short periods of 8 to 12 weeks in patients with nephrotic range proteinuria. Up to almost 70 percent of patients with NS-associated FSGS may attain complete or partial remission and maintain stable renal function for about 10 years when given a prolonged therapy with steroid or immunosuppressive drugs (19). Our patient achieved partial proteinuric remission after 5 months of therapy, but did not gain complete remission till follow-up at 9 months.

In conclusion, renal replacement therapy may be required in cases of idiopathic NS-associated ARF secondary to FSGS, especially when it is severe enough to cause persistent oliguria and accumulation of nitrogen products. These patients are sensitive to steroid therapy; therefore, it should be initiated as promptly as possible and treatment duration should be prolonged for better benefits. Consequently, the reversibility of ARF might be expected as in our patient.

References

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