CASE REPORT

DOI: 10.5336/caserep.2022-89530

Severe Acute Kidney Injury in a Child with Nephrotic Syndrome

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This study was presented as a poster at the 53rd ESPN Annual Meeting, September 16-19 2021, Amsterdam, Netherlands.

ABSTRACT Nephrotic syndrome (NS) may have complications like infection, thromboembolism, acute kidney injury (AKI) and hypovolemia in children. However, severe AKI with anuria is unusual and rarely reported. In this study, 9 year-old girl hospitalized with first episode of NS after recent antibiotic and ibuprofen use was presented. Despite albumin and furosemide, as she became anuric on the third day of hospitalization, hemodialysis was started and pulse methylprednizolone was given. Renal biopsy revealed minimal mesangial proliferation with widespread acute tubular injury findings. She was discharged at the 15th day with normal urine volume after 11 hemodialysis sessions. After six weeks of oral prednisolone, complete remission in NS was achieved. Acute tubular necrosis was the underlying diagnosis for anuric AKI in the setting of NS. Heavy proteinuria leading to tubular obstruction, presence of decreased effective intravascular volume due to severe hypoalbuminemia, and ibuprofen use may have caused acute tubular necrosis.

Keywords: Nephrotic syndrome; acute kidney injury; anuria; acute tubular necrosis; children

Idiopathic nephrotic syndrome (INS) is a common glomerular disorder in childhood.[1,2] Main complications are infection, thromboembolism, acute kidney injury (AKI) and hypovolemia. AKI in INS is associated with high morbidity and even mortality. There is often modest renal dysfunction in these patients due to decreased glomerular capillary wall permeability to creatinine, that is usually reversible with remission.[2,3] Although children with NS have higher AKI risk because of bilateral renal vein thrombosis, intravascular volume depletion, tubular obstruction with protein casts, acute tubulointerstitial nephritis (TIN), nephrotoxic medications and acute tubular necrosis (ATN) secondary to sepsis or hypovolemia, a very severe course with need for renal replacement therapy is quite uncommon.[2,4-6] Herein, a girl with NS who developed severe anuric AKI and underwent dialysis is presented.

CASE REPORT

Nine year-old previously healthy girl was brought to the general practitioner with high fever and cough. Amoxicillin-clavulanate (60 mg/kg/day) and ibuprofen (20 mg/kg/day) were given for acute pharyngitis. Fever subsided after two doses of ibuprofen. On the fourth day of the antibiotic treatment however, swelling in her eyes was noticed. As the urine analysis revealed 3+ proteinuria, she was referred to our hospital. On admission, she had no macroscopic hematuria or decrease in urine amount. Body weight: 32.8 kg (measured as 29 kg two weeks ago), blood pressure: 110/72 mmHg (<90p) was noted. She had hyperemic tonsils, purulent postnasal drainage, prominent periorbital and pretibial edema and mild ascites.

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Peer review under responsibility of Turkiye Klinikleri Journal of Case Reports.

Received: 10 Mar 2022 ***Received in revised form:*** 14 Sep 2022 ***Accepted:*** 19 Sep 2022 ***Available online:*** 21 Sep 2022

Complete blood count was normal. Acute phase reactants were moderately elevated [C-reactive protein: 29 mg/dL (0-5.0), erythrocyte sedimentation rate: 52 mm/h (0-20)]. Blood chemistry showed blood urea nitrogen: 45 mg/dL, creatinine: 1.07 mg/dL, albumin: 1.7 g/dL, uric acid: 5.7 mg/dL. She had hyperlipidemia (total cholesterol: 326 mg/dL, triglyceride: 208 mg/dL). Coronavirus disease-2019 polymerase chain reaction was negative. Urine analysis demonstrated specific gravity: 1040, 4+ proteinuria and microscopic hematuria (erythrocytes: 12/high-power field). Nephrotic range proteinuria (spot urine protein/creatinine ratio: 27 mg/mg) was detected. She was hospitalized with fulfilling the NS criteria. Treatment on admission (hospital day 1) consisted of continuation of amoxicillin-clavulanate. Oral prednisolone was planned to be initiated after the upper respiratory tract infection subsided. She had two episodes of vomiting and daily maintenance fluid was replaced intravenously. On the second day, she had oliguria (0.5 mL/kg/h) and increased creatinine levels (2.32 mg/dL) with decline in serum albumin (1.5 g/dL). Albumin infusion (0.5 g/kg/day) and intravenous furosemide (1 mg/kg/day) were administered. However, urine output further decreased. At the third day, she became hypertensive and anuric (0.3 mL/kg/h) with serum creatinine: 4.18 mg/dL. Conventional hemodialysis was started. Renal biopsy was performed for the clinical suspicion of rapidly progressive glomerulonephritis. Pulse intravenous methylprednisolone (30 mg/kg/day for three consecutive days) was given. Amlodipine 0.2 mg/kg/day was given to control hypertension. Abdominal ultrasonography (USG) revealed Grade 1 echogenic, normal sized kidneys. Renal Doppler USG ruled out renal vein thrombosis. Serum complement (C3 and C4), immunglobulin A levels were normal. Viral and bacterial serologies were negative. Anti-nuclear antibody was 1+, anti-dsDNA, antineutrophil cytoplasmic autoantibodies and anti-glomerular basement membrane antibodies were all negative. Renal biopsy demonstrated normal histology in the majority of 43 glomeruli, except minimal mesangial proliferation in few remaining glomeruli. However, widespread acute tubular injury was present (Figure 1, Figure 2). Immunofluorescence examination was negative. Following three courses of intravenous methylprednisolone, oral prednisolone was started (2 mg/kg/day). As she remained completely anuric for the following four days, necessity for hemodialysis persisted. At the 11th day, urine output restarted and gradually increased. At the 15th day, serum creatinine decreased to 1.79 mg/dL, she became normotensive with increased urine output (4.4 mL/kg/h). Hemodialysis was stopped after 11 sessions and she was discharged safely. At the 6th week, she had normal serum creatinine (0.45 mg/dL), albumin (4 g/dL), spot urine protein/creatinine (0.13 mg/mg). Steroids were given for overall five months. After one year, she was in complete remission. Laboratory findings and treatment protocols are demonstrated in Table 1. Informed consent was obtained from the parents for reporting the case.

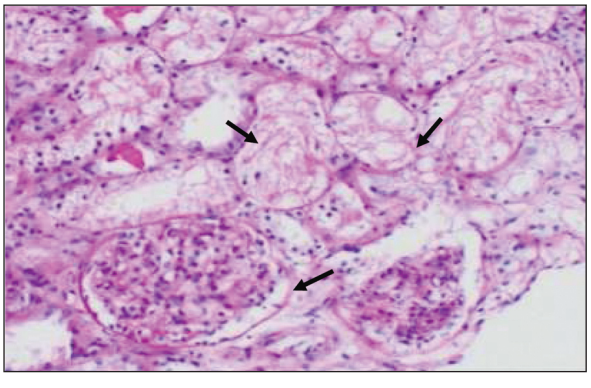

FIGURE 1: Light microscopy showing normal glomerular morphology (lower arrow) and diffuse tubular injury (upper arrows) (H&E; x200).

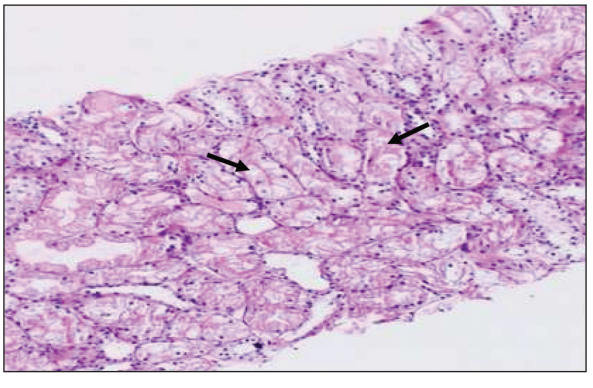

FIGURE 2: Findings of acute tubular necrosis in renal biopsy (arrows) (H&E; x100).

TABLE 1: Laboratory findings and treatment protocols.

Treatment days	Serum creatinine (mg/dL)	Serum albumin (g/dL)	Proteinuria (spot or 24 hour urine)	Urine amount	Treatment protocol
Admission	1.07	1.7	27 mg/mg	NA	Oral antibiotic
Day 2	2.32	1.5		0.5 mL/kg/h	Albumin+furosemid
Day 3	4.18	2.8		0.3 mL/kg/h	HD+Pulse MPZ+AML
Day 4	3.39	2.6		20 mL/d	HD+Pulse MPZ+AML
Day 5	2.79	2.6		-	HD+Pulse MPZ+AML
Day 6	2.45	2.4		-	PRZ+AML
Day 7	3.76	2.2		-	HD+PRZ+AML
Day 8	2.88	2.2		-	HD+PRZ+AML
Day 9				-	HD+PRZ+AML
Day 10	4.64	2.4		-	HD+PRZ+AML
Day 11				20 mL/d	HD+PRZ+AML
Day 12	3.44	2.4		0.8 mL/kg/h	HD+PRZ+AML
Day 13	4.09	2.6		1.3 mL/kg/h	HD+PRZ+AML
Day 14	2.15	2.4		1.9 mL/kg/h	HD+PRZ
Day 15	1.79	2.6		4.4 mL/kg/h	PRZ
Day 29	0.57	3.9	16 mg/m^2/h	2.4 mL/kg/h	PRZ
Day 43	0.45	4.4	0.3 mg/mg		PRZ tapering
3rd month	0.43	4.6	4.5 mg/m^2/h	2.5 mL/kg/h	PRZ tapering
5th month	0.51	4.3	0.16 mg/mg		PRZ cessation
10th month	0.46	4.3	3.9 mg/m^2/h		-

NA: Not available; HD: Hemodialysis; MPZ: Methylprednisolone; PRZ: Prednisolone; AML: Amlodipine.

DISCUSSION

AKI is an alarming complication of INS associated with high morbidity including lower rates of complete remission, risk of progression to chronic kidney disease, and even mortality.[2,4,7] Therefore, careful evaluation of the children with INS in terms of AKI is important. AKI in INS was uncommon in earlier studies (0.8-8%).[2,8,9] However, Rheault et al. showed AKI incidence of 58.6% in 336 children with INS.[6] 158% increase in the frequency of INS hospitalizations complicated by AKI between 2000-2009 was also reported.[10] Such differences are possibly linked to different AKI definitions in the early studies.

Histopathologic diagnosis underlying anuric AKI in our patient was ATN. It is a significant complication in patients with INS, occurring due to hypovolemia with hypoalbuminemia, often exacerbated by excessive diuresis.[3] In our patient, daily fluids were replaced intravenously for preserving the blood volume. Diuretics were applied only once following albumin replacement. Therefore, aggressive diuresis in the context of hypovolemia is not the point for our case.

Three mechanisms are suggested in the etiology of ATN in this patient. Firstly, despite interventions towards preserving the blood volume, severe hypoalbuminemia may have led to decreased plasma oncotic pressure, which decreased effective circulatory volume and progressed into ATN. Secondly, massive proteinuria (spot urine protein/creatinine ratio: 27 mg/mg) at admission is believed to contribute, as heavy glomerular albumin leakage could lead to tubular obstruction with protein casts and presence of interstitial edema (so-called "nephrosarca") may result in tubular collapse.[2,3,11] Lastly, ibuprofen, a nonsteroid anti-inflammatory drugs (NSAIDs), can be associated with AKI either by causing ATN or acute TIN.[12,13] Dixit et al. showed that significant AKI developed (with dialysis need in 2 cases and acute TIN in 5 cases) after NSAID use in 15 children with normal kidney functions. Moreover, one patient had full-blown minimal change NS (MCNS) accompanied by acute TIN.[13] ATN in NSAID users may develop

through alterations in blood flow mediated by decreased prostaglandin synthesis especially in patients with compromised renal perfusion.[12] We believe that combination of several risk factors induced severe anuric AKI due to ATN, rather than considering single specific entity in our patient.

Nephrotic syndrome beyond infancy is mostly idiopathic and MCNS is responsible for over 80%. However, it can be secondary to systemic disorders including infections, vasculitis, malignancies and drugs (including NSAIDs).[1] We believe that ibuprofen use has played significant role in ATN development in our case. This made us consider if this drug use triggered NS clinical picture itself. NSAIDs could induce a "pure NS".[14] Robinson et al. reported MCNS (accompanied by acute TIN in one case) in two children with long-term NSAID use.[15] In our patient, NS emerged only four days after ingesting two doses of ibuprofen. Acute TIN was not detected on renal biopsy. Attribution of clinical picture of NS to ibuprofen use is among the possibilities.

Although the burden of AKI in NS appears to be recently increased, severe AKI necessitating dialysis is still rare.[6] However, mean time to renal function recovery was longer in patients with more severe AKI.[4] Additionally, 41.2% of the children with INS had varying degrees of chronic kidney disease in long-term.[7] Our patient had severe AKI requiring 11 hemodialysis sessions. Renal functions were completely normalized on the 15th day. Fortunately, no long-term sequela was detected so far.

In conclusion, the presentation of our patient highlights the importance of awareness about the possibility of severe AKI in NS for initiating prompt therapy and preventing critical complications.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Bahar Büyükkaragöz, Burcu Yazıcıoğlu;* ***Design:*** *Bahar Büyükkaragöz, Burcu Yazıcıoğlu;* ***Control/Supervision:*** *Sevcan Azime Bakkaloğlu, Oğuz Söylemezoğlu;* ***Data Collection and/or Processing:*** *Bahar Büyükkaragöz, Burcu Yazıcıoğlu;* ***Analysis and/or Interpretation:*** *Bahar Büyükkaragöz, Sevcan Azime Bakkaloğlu, Oğuz Söylemezoğlu;* ***Literature Review:*** *Burcu Yazıcıoğlu;* ***Writing the Article:*** *Bahar Büyükkaragöz, Sevcan Azime Bakkaloğlu;* ***Critical Review:*** *Necla Buyan;* ***References and Fundings:*** *Necla Buyan;* ***Materials:*** *Sevcan Azime Bakkaloğlu.*

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