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BRIEF REPORT

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Peritonitis as a risk factor of acute renal failure in nephrotic children

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Abstract Idiopathic acute renal failure (IARF) is an uncommon but severe complication in children with relapsing nephrotic syndrome and may require long-term dialytic support until recovery of renal function takes place. Due to limited understanding of the pathophysiology of IARF, specific guidelines for its prevention and therapy have not been developed. Among triggering factors, peritonitis was present in half of all pediatric patients with this complication described in the English literature over the past 15 years. We report an additional nephrotic child who developed IARF following spontaneous bacterial peritonitis. The renal biopsy showed tubular epithelial changes consistent with acute tubular necrosis. A discussion of related literature and possible pathogenesis of this association is presented.

Key words Nephrotic syndrome · Acute renal failure · Children · Peritonitis · Ischemic tubular necrosis

Introduction

Low urine output and mildly reduced glomerular filtration rate are common in patients during relapses of idiopathic nephrotic syndrome [1]. However truly acute "intrinsic" renal failure is an uncommon complication of this disease, especially in children [1, 2, 3, 4]. A clear explanation for the development of severe renal failure in these patients is rarely found, but in most cases clinical improvement with supportive therapy suggests unknown and transient deleterious phenomena. Occasionally, concomitant infections have been proposed, but their pathogenic role is not clear [2]. We present a case of idiopathic acute renal failure (IARF) following primary peritonitis in a child with relapsing minimal-change nephrotic syndrome (MCNS). Related literature and possible pathogenesis of IARF are discussed.

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Case report

A 4-year-old boy with frequent relapsing steroid-responsive nephrotic syndrome was admitted to the pediatric unit with a history of 2 days of generalized edema, abdominal pain, diarrhea, and fever. His nephrotic syndrome had been diagnosed 2 years previously. When symptoms started, the patient was on neither steroids nor immunosuppressive therapy. On admission his weight was 17.8 kg, 3 kg over the last recorded weight (1 month previously), supine blood pressure 110/50 mm Hg, heart rate 158 bpm, and axillary temperature 40°C. Physical examination showed marked periorbital and pretibial edema as well as moderate ascites. His abdomen was diffusely tense and painful on palpation, with no audible bowel sounds. Admission laboratory tests showed Na 131 mmol/l, K 4.63 mmol/l, Cl 104 mmol/l, HCO_3 19 mmol/l, calcium 7.3 mg/dl, phosphorus 5.2 mg/dl, albumin 0.7 g/dl, glucose 192 mg/dl, BUN 12 mg/dl, creatinine 0.3 mg/dl, cholesterol 561 mg/dl, hematocrit 38%, WBC 22,800 with 17% bands, ESR 107 mm/h and C-reactive protein 1.1 mg/dl. Urinalysis showed protein 4+, glucose +, RBC 100/hpf (nondysmorphic), WBC 10/hpf, 10–15 hyaline, granular and waxy casts/hpf. Due to suspected peritonitis, a diagnostic peritoneal tap was performed. A sample of yellowish fluid was obtained, having WBC 320/mm^3 (80% neutrophils) and gram-positive diplococcus. The patient was started on i.v. sodium penicillin, gentamicin, and infusion of salt-poor 20% albumin (1 g/kg) followed by i.v. furosemide (1 mg/kg). Twenty-four hours after admission, the patient was started on i.v. hydrocortisone 30 mg qid. Gentamicin was discontinued once peritoneal and blood culture results confirmed the presence of *Streptococcus pneumoniae*. Urine, pharyngeal, and stool cultures were negative. For several days the urine output remained low (less than 0.7 cc/kg/h) despite infusions of albumin plus furosemide. Serum creatinine and BUN increased (Fig. 1) and diastolic blood pressure rose to the 80s. On day 7, the patient's clinical status deteriorated, with respiratory distress, arterial hypertension of 140/90 mm Hg, oligoanuria despite diuretics, and progressive edema. At that time serum albumin was 2.9 g/dl and total protein was 4.7 g/dl. Chest X-ray was compatible with pulmonary edema, and the patient was transferred to the pediatric intensive care unit, requiring intubation and mechanical ventilation. Renal ultrasound showed large kidneys with diffusely increased parenchymal echogenicity, patent vascular renal flow, and no dilation of pelves and ureters. MAG-3 renal scintigraphy showed good uptake but poor

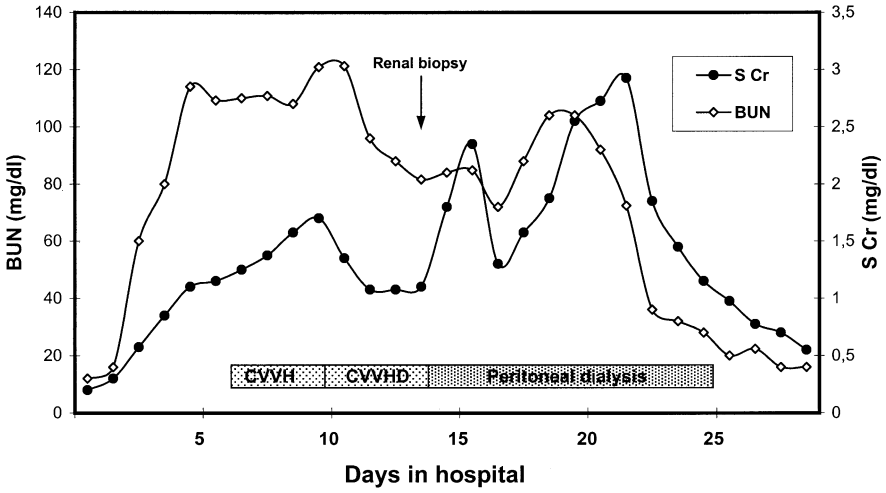

Fig. 1 Changes in blood urea nitrogen and serum creatinine during hospitalization. Dialytic therapies are shown in *horizontal bars* below the *curve*. *BUN* blood urea nitrogen, *S Cr* serum creatinine, *CVVH* continuous veno-venous hemofiltration, *CVVHD* continuous veno-venous hemodiafiltration

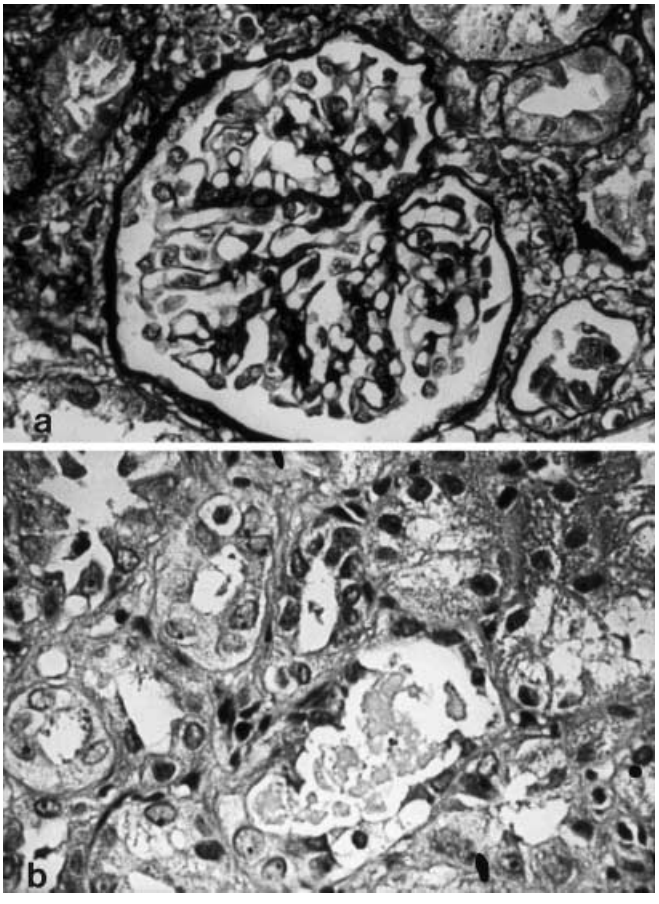

Fig. 2a,b Renal histology. **a** Normal glomerulus with mild accentuation of mesangium. **b** Tubules with scattered tubular cell necroses, interstitial edema, scant lymphohistiocytic infiltrate, attenuation of tubular epithelium, hydropic vacuolar degeneration, and proteinaceous casts, compatible with acute tubular necrosis

excretory phase, consistent with acute renal insufficiency. Several hours later, the patient was started on continuous veno-venous hemofiltration, then on a sodium nitroprusside drip, due to arterial hypertension unresponsive to intravascular volume correction. The serum albumin and total protein remained unchanged compared with those previously described (2.9 and 4.8 g/dl, respectively). Because of persistently increasing plasma levels of BUN and creatinine, he was switched to continuous hemodiafiltration, and nitroprusside was changed to i.v. labetolol. On day 14, the patient was extubated, and hemofiltration was discontinued. He was switched to peritoneal dialysis (PD). During the PD Tenckhoff catheter placement, a percutaneous renal biopsy was performed, which showed essentially normal glomeruli with attenuation of the foot processes of the podocytes and tubular damage consistent with moderate to severe acute tubular necrosis (Fig. 2). He was kept on PD for 11 days, until spontaneous recovery of renal function and adequate urine output with low-dose diuretics were achieved. The patient was discharged from hospital on day 31 post admission on prednisone (2 mg/kg/d) and slow-release nifedipine (10 mg bid). Serum creatinine was 0.4 mg/dl and albumin 3.4 g/dl. His urinalysis showed no proteinuria. At follow- up 1 year later, he had normal arterial pressure and renal function, without evidence of nephrotic relapse.

Discussion

IARF is a well-recognized but uncommon clinical event in nephrotic patients, first described over 30 years ago in an adult population [5]. Since then, fewer than 100 patients have been reported in the English-language medical literature, with a clear prevalence (90.7%) among individuals older than 18 years [2]. Its pathogenesis is poorly understood. Apart from some cases in which a clear explanation for renal insufficiency was found (e.g., bilateral renal vein thrombosis, severe intravascular depletion or concomitant shock, pyelonephritis and drug-induced nephrotoxicity), many cases have not disclosed a clear cause for the renal insufficiency, as with the one presented here. Possible explanations proposed have included unrecognized hypovolemia, tubular obstruction, altered glomerular permeability, preexisting intrinsic glomerular abnormalities, interstitial edema, and/or marked expression of poorly understood hemodynamic factors decreasing the glomerular filtration rate in several relapsing nephrotic patients [1, 2, 4]. Interestingly, and contrary to the traditional view of nephrotic patients as "hypovolemic", apparently only one third of them were intravascular volume depleted at the time of relapse [6].

It is not known if only hypovolemic nephrotic patients may develop IARF, but the response to volume challenge in such cases has been rather erratic, supporting the hypothesis of intrarenal hemodynamic changes as the most important causes of renal ischemia [1]. In any event, a close estimation of intravascular volume and serum albumin/total protein should be made before a volume challenge is attempted.

The incidence of IARF among children with nephrotic syndrome has been reported as close to 5% [3], but this may not be accurate, considering the scarcity of cases diagnosed and published. In the past 15 years, only eight nephrotic children (<18 years) developing IARF have been reported in the English literature, as shown in a recent review [2]. Of these eight patients (mean age 9±3 years), 57.1% had MCNS on renal histology. Six of the eight patients required dialysis, with recovery of renal failure and 100% survival. Interestingly, in four of them (50%) peritonitis was the triggering event [2].

Primary peritonitis is a relatively common complication of relapsing nephrotic syndrome in childhood, with a reported incidence of between 5 and 17.3% [7, 8]. *S. pneumoniae* is usually the main causative agent (in close to 50% of cases), followed by gram-negative enterobacteria (i.e., *Escherichia coli*) [7, 9]. Besides the immunosuppressive effect of steroids, risk factors for severe infections in MCNS patients are low levels of serum immunoglobulins [10] and specific deficits of intermediary components of the complement cascade, as demonstrated for factors I and B [11].

In the present case, as in half of the children with IARF described above, peritonitis was strongly associated with the development of this complication. Why is this so? Assuming that patients in nephrotic relapse are already at risk for IARF, as noted above, added peritonitis may worsen the intra- and extrarenal hemodynamics through elevated intraperitoneal production (and subsequent absorption) of deleterious cytokines such as tumor necrosis factor-α and interleukin-6 [12, 13]. In addition, peritoneal inflammation and exudation may increase third-space (intraperitoneal and intraintestinal) volume sequestration, thus aggravating low intravascular volume. So far, a direct effect of ascites on renal function in noncirrhotic patients has not been clearly demonstrated, but sustained increase in intra-abdominal pressure may cause renal dysfunction as part of the abdominal compartment syndrome, which has been described following a series of insults, including severe abdominal trauma, ruptured aortic aneurysm, and intra-abdominal infection [14].

The potential reversibility of this form of renal failure should be considered when long-term plans are made for its management and the patient's prognosis. As occurred in the present case, renal histology usually shows abnormalities of the tubulointerstitium consistent with acute tubular necrosis and marked interstitial edema, as well as glomerular changes corresponding to the renal disease causing the nephrotic relapse, most commonly MCNS [1]. This fact highlights the importance of early renal biopsy in these patients, making it possible to rule out other entities mimicking the presented picture, e.g., rapidly progressive glomerulonephritis [15]. In the case presented here, the biopsy was deferred to the end of the second week because of the high risk of renal bleeding in a hypertensive child receiving heparin due to the hemofiltration procedure.

Therapeutic means of avoiding IARF in nephrotic patients are poorly defined, and specific recommendations have not been established. The risk of IARF may be minimized (a) by avoiding the development of frank edema and ascites with sodium restriction (and judicious initiation of steroid treatment) once the nephrotic relapse is evident; (b) by careful management of fluid infusion in order to maintain an adequate intravascular volume, particularly when a patient has peritonitis; and (c) by careful use of drugs that have nephrotoxic or hemodynamic effects. Immunization against *S. pneumoniae* may be the indicated prophylaxis against the most common cause of spontaneous peritonitis [16], considering that infection is the leading cause of death among children with MCNS [17].

In brief, this case illustrates that acute renal failure is a rare but severe complication in children with relapsing MCNS and should be kept in mind particularly when peritonitis is present. IARF is frequently reversible even after prolonged renal replacement therapy.

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LITERATURE ABSTRACTS

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WT1 splice-site mutations are rarely associated with primary steroid-resistant focal and segmental glomerulosclerosis

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Background Donor splice-site de novo heterozygous mutations in intron 9 of the Wilms' tumor gene (WT1) have been reported in Frasier syndrome, which is defined by the association of focal and segmental glomerulosclerosis (FSGS), male pseudohermaphroditism, and gonadoblastoma. These splice-site mutations alter the WT1 alternative splicing leading to two WT1 isoforms, with (+) or without (–) three amino acids, lysine-threonine-serine (KTS), between zinc fingers 3 and 4. The aim of this work was to investigate the possibility that some cases of primary steroid-resistant nephrotic syndrome associated with FSGS may be caused by WT1 splice-site mutations.
Methods We analyzed WT1 exons 8 and 9 and the surrounding exon/intron boundary DNA sequences in 37 children with nonfamilial primary steroid-resistant nephrotic syndrome. Semiquantitative reverse transcription-polymerase chain reaction (RT-PCR) was used to determine the relative ratio of +KTS/–KTS transcripts from immortalized lymphocyte RNA.
Results One boy with FSGS and associated pathologies (diaphragmatic hernia, proximal hypospadias, and unilateral testicular ectopia) was found to carry the heterozygous 1228 +4 C–>T splice-site mutation. RT-PCR quantitation of the +KTS/–KTS transcripts from immortalized lymphocyte RNA of this patient showed a diminution of the +KTS/–KTS isoform ratio (0.43), which is identical to that reported in patients with Frasier syndrome. Using the same approach, healthy control subjects have +KTS/–KTS ratios ranging from 1.50 to 2.00.
Conclusions This study expands the range of the phenotypic presentation of the intron 9 splice-site WT1 mutations and adds to the already reported heterogeneity of primary steroid-resistant nephrotic syndromes. We suggest that these mutations are not likely to be a common cause of isolated steroid-resistant nephrotic syndrome, and recommend a WT1 exon 9/intron 9 splice-site study in children with primary steroid-resistant nephrotic syndrome if genital or diaphragmatic anomalies are associated. The identification of such WT1 mutations has practical implications for the management of these patients.

M.M. Ward

Outcomes of renal transplantation among patients with end-stage renal disease caused by lupus nephritis

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Background Although the outcomes of renal transplantation among patients with end-stage renal disease (ESRD) caused by lupus nephritis have generally been found to be comparable to those of patients with other causes of ESRD, some studies indicate that cadaveric graft failure is more common among these patients. However, most previous studies examined small numbers of patients and did not adjust for important confounding factors.
Methods Graft failure and patient mortality after the first cadaveric renal transplantation were compared between 772 adults with ESRD caused by lupus nephritis and 32644 adults with ESRD caused by other causes who received a transplant between 1987 and 1994 and were included in the United States Renal Data System. The median follow-up times were 4.9 and 5.0 years in the two groups, respectively. Multivariate Cox regression models were used to adjust the risks of graft failure and mortality for group differences in recipient and donor characteristics. Similar comparisons were performed between 390 adults with ESRD caused by lupus nephritis and 10512 adults with ESRD caused by other causes after first living-related renal transplantation.
Results In an unadjusted analysis, the risk of graft failure after first cadaveric transplant was slightly but significantly greater among patients with ESRD caused by lupus nephritis than among those with ESRD caused by other causes [hazard ratio (HR), 1.13; 95% CI, 1.01 to 1.26, P=0.04]. However, after adjustment for potential confounding factors, the risk of graft failure was not increased in patients with ESRD caused by lupus nephritis (HR, 1.08; 95% CI, 0.94 to 1.23, P=0.28). Mortality after the first cadaveric transplantation did not differ between groups. The adjusted risks of graft failure (HR, 1.06; 95% CI, 0.84 to 1.32, P=0.62) and patient mortality (HR=0.69; 95% CI, 0.45 to 1.05, P=0.09) after the first living-related renal transplant were also not significantly higher among patients with ESRD caused by lupus nephritis.
Conclusions Graft and patient survival after first cadaveric and first living-related renal transplants are similar in patients with ESRD caused by lupus nephritis and patients with ESRD from other causes.