Multiple Causes of Renal Functional Deterioration in Bladder Rhabdomyosarcoma: Case Report

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Introduction
During the last 2 decades, studies involving genitourinary rhabdomyosarcoma showed 5-year survival rates reaching over 70% with the addition of multimodal therapy (1). However, the nephro-urological morbidity of the rhabdomyosarcoma of the lower genitourinary tract is related to renal and urological functions. The mass effect of the tumor may result in complications related to obstructive uropathy (2). The use of various chemotherapeutic agents may also result in persistent or even progressive kidney dysfunction in the form of tubular damage or chronic impairment of glomerular function (3). Nephrotoxic antinfecive drugs used during episodes of febrile neutropenia and culture proven infections may contribute to renal sequelae. Breakthrough urinary tract infections or other prerenal triggers of renal function may lead to permanent renal
functional loss. Surgical procedures that involve partial or total cystectomy and bladder augmentation may contribute to urological problems in the form of small reservoir capacity, incontinence or recurrent urinary tract infections (4).

In this case report, we describe a patient of bladder rhabdomyosarcoma who presented with acute renal failure and progressed to chronic renal failure. Factors related to renal functional loss are discussed.

**Case Report**

An 8-month-old boy was referred to our hospital because of severe difficulty in urination. On physical examination hypertension (blood pressure 220/120 mmHg) and distended abdomen with a palpable suprapubic mass were found. Laboratory investigations revealed metabolic acidosis (pH: 6.9, HCO₃: 3 mEq/L) and impaired renal function tests (BUN: 207 mg/dL, creatinine: 3.7 mg/dL). Ultrasonographic (USG) and computerized tomographic investigations showed bilaterally grade IV hydronephrosis and a 45x40 mm mass in bladder (Figure 1, Figure 2a and 2b). Hydronephrosis was treated immediately with bilateral temporary nephrostomies. The cystoscopic biopsy of the mass revealed embryonal rhabdomyosarcoma with polypoid features infiltrating the trigonal area which is localized at posteroinferior wall of the bladder. As staging evaluations including radionuclide bone scan and bone marrow biopsy were negative, tumor was classified as group III stage IIIa according to Intergroup Rhabdomyosarcoma Study (IRS) Staging System. Antihypertensive medication was initiated with nifedipine and captopril. Renal function tests improved and serum creatinine decreased to 0.7 mg/dL after 4 days of the relief of obstruction. Chemotherapy was commenced according to IRS D9803, standard regimen with vincristine, actinomycin D and cyclophosphamide every 3 weeks for a total of 42 weeks. The child was followed periodically by repeated USG and computerized tomography examinations. The mass in the bladder showed a reduction close to
50% in size on the 12th week of chemotherapy. At this time total removal of the tumor that still infiltrates the trigonal area was not considered to be possible without a debilitating surgery. Adjuvant radiotherapy to the pelvis (180 cGy in 28 fractions for a total of 5040 cGy with 6 MV) was given. Hydronephrosis decreased to grade II gradually and nephrostomy tubes were taken off on the 22nd week of chemotherapy. After the removal of nephrostomy tubes no increase in the degree of hydronephrosis was observed for the first 3 months. Afterwards on the 34th week of chemotherapy the boy experienced two temporary obstructive episodes during urinary tract infections diagnosed by USG. During the 38th week of chemotherapy, gross hematuria leading to severe drop in hemoglobin levels that did not resolve or improve with bladder irrigations occurred. As a result radical cystectomy and bilateral ureterocutaneostomy were performed. The pathological examination of the bladder showed diffuse fibrosis and tumor infiltration which was attributed as the cause of gross hematuria. In postoperative 1st week the boy had a severe attack of obstruction and cessation of diuresis on the right side that was treated with replacement of a right nephrostomy tube. Six months after the first surgery definitive surgery of urinary diversion by a colonic conduit and an ileal tunnel was performed and clean intermittent catheterization 4 times a day was initiated. Time courses of clinical events are shown on Figure 3.

The patient experienced several urinary tract infection episodes during his chemotherapy. Im-

![Figure 3. Time course of clinical events.](image-url)
immune suppressive drugs, nosocomial infections, febrile neutropenic episodes could be considered as the predisposing factors. The first renal Tc99m dimercaptosuccinic acid (DMSA) scan performed at the age of 1 year showed no evidence of scaring and the first voiding cistourethrogramy (VCUG) did not show vesicoureteral reflux. Two and 5 months after the cessation of chemotherapy, the patient experienced prerenal acute renal failure twice, one because of acute gastroenteritis and the second as a result of bronchiolitis which both caused severe dehydration and increase in serum creatinine levels.

Control DMSA scan performed at the age of 2 9/12 years after multiple urinary tract infections showed a cortical defect on the superior pole of the right kidney and a decrease in the total renal uptake of DMSA with increased activity in ileocolonic conduit (Figure 4). However, increased spleen and liver activity was not observed. VCUG performed at the same time revealed grade IV vesicoureteral reflux on the right side (Figure 5) and the clean intermittent catheterization was increased to 6 times a day.

During nephrological follow-up, a gradual increase in serum creatinine levels was observed: 0.3 mg/dL (10 months of age), 0.5 mg/dL (15 months of age), 0.8 mg/dL (2 years of age), 0.8 – 1 mg/dL (3 years of age) and glomerular filtration rate decreased to 66 mL/min/1.73 m² (27 months of age) from 80 mL/min/1.73 m² (12 months of age). Separated renal functional glomerular filtration rates were 10 mL/min/1.73 m² for right side and 51 mL/min/1.73 m² for left side measured by urine collected from each side by ureterocutaneostomy drainage. His final GFR at the age of 3 years was 47 mL/min/1.73 m² (Figure 3). His biochemical parameters showed transient hypophosphatemia (2.5 mg/dL, 4.5 mg/dL), hypokalemia (2.8 mEq/L, 3.2 mEq/L, 3.9 mEq/L) and urinalysis showed a pH of 7, specific gravity of 1006, and proteinuria (27 mg/m²/hr, 87 mg/m²/hr). The distribution of proteins detected in urine were albumine 38%, alpha 1 globuline 18%, alpha 2 globuline 12% and beta globuline 12%. Tubulary functional tests of phosphate reabsorption was 80% and normal urinary calcium, sodium and potassium excretion were found.

Currently, the patient has no signs of tumoral recurrence 18 months after cessation of chemotherapy, is performing clean intermittent catheterization and has asymptomatic bacteriurias with a creatinine clearance of 47 mL/min/1.73 m².

**Discussion**

Genitourinary tumors are very rare in childhood and they should be kept in mind during the differential diagnosis of obstructive renal failure. Our case has an obstructive acute renal failure and the relief of the obstruction dramatically reversed the impaired renal functions. However, during follow-up
multiple episodes of urinary tract infections with attacks of temporary obstruction and the administered nephrotoxic drugs, ultimately resulted in renal functional deterioration.

Recurrent urinary tract infections unless treated early and properly may become dangerous if ascending bacteria reach the kidney and induce an inflammatory reaction within the renal parenchyma. The inflammatory reaction may result in renal scar formation leading to reduced renal function (5). Our patient experienced several episodes of nosocomial urinary tract infections during febrile neutropenic attacks and surgical procedures although there was no anatomical anomaly such as vesicoureteral reflux. These infections were treated with wide spectrum antibiotics and antifungal drugs such as vancomycin, teicoplanin, meropenem, cefepime, ciprofloxacin, amikacin, nitrofurantoin, amphotericin B. The first DMSA scan performed after the first urinary tract infection at the age of 1 year revealed no evidence of scarring or reduction in total DMSA uptake. The last DMSA scan performed at the age of 2 9/12 years showed a cortical defect on the superior pole of the right kidney. Studies have shown that renal scars especially following urinary tract infection with vesicoureteral reflux are the main causes of chronic renal failure (5). Our case experienced several episodes of urinary tract infections during hospitalization and were all treated with proper antibiotics according to urine culture sensitivity tests. A VCUG performed 6 months after the definitive surgery of urinary diversion showed grade IV reflux on the right side. Although the right kidney scar detected on DMSA is not the sole cause, it may be one of the contributing factors to renal functional loss.

The second contributing factor to renal functional loss is temporary obstructive attacks. Obstruction of the urinary tract is a frequent cause of transient renal dysfunction that is reversible in the majority of cases (6). Our case has also presented with acute obstructive renal failure and relief of the obstruction resulted in improvement of diuresis and renal functional tests.

Beyond these acute problems, obstructive uropathy may occasionally result in progressive irreversible loss of nephrons with renal parenchyma being replaced by extracellular matrix causing chronic renal failure due to chronic tubulointerstitial nephritis (6,7). If both kidneys are affected, the result would be end stage renal disease (7). The exact prognosis depends on the cause and the duration of the obstruction, and the presence or absence of urosepsis (7). However, the degree of functional recovery following relief of obstruction is difficult to predict. Our patient experienced several attacks of obstruction after the removal of nephrostomy tubes. Pelvicalyceal system and renal tissue edema and urinary stasis might have occurred as a result of breakthrough urinary tract infections, leading to an increase in the degree of hydronephrosis (6,7). After radical cystectomy and ureterocutaneostomy, the boy experienced a severe attack of obstruction on the right side. Grade IV hydronephrosis causing parenchymal thinning was treated by replacement of a right nephrostomy tube. Placement of nephrostomy tubes resulted in the reduction of degree of hydronephrosis but probably some degree of renal functional loss had occurred, in the meantime.

Our patient did not experience symptomatic urinary tract infection after the operation of diversion by colonic conduit despite the development of right vesicoureteral reflux. Clean intermittent catheterization enabled the complete emptying of the reservoir. He has been under trimethoprim/sulfamethoxazole prophylaxis and has been followed by routine urine culture tests performed every month. Although application of colonic conduit and an ileal stoma offers good prospects of a socially acceptable life with preservation of renal function, permanent deviation of the urinary stream places a heavy burden on the child and his caregivers. A successful continent deviation saves the trouble of continuously wearing a device and the associated risks of leakage and odor (8). Regularly performed clean intermittent catheterization is necessary for the success of continence.

Another factor for renal functional impairment is breakthrough episodes of prerenal acute renal failure. Our patient experienced two episodes of infections leading to severe dehydration and increase in serum creatinine concentrations. After the treatment of infections and dehydration, serum creatinine levels remained higher than the baseline values.

The fourth contributing factor to renal functional loss is the use of multiple nephrotoxic drugs. Cephalosporins, quinolones, penicillins cause acute in-
terstitial nephritis due to immunologic effects (9). Aminoglycosides, amphotericin B and cephalosporins may cause tubulotoxicity (10). Cyclophosphamide therapy also increased the amount of damage to the renal tissue. Cyclophosphamide chemotherapy is associated with nephropathy characterized by glomerular and tubular toxicity (11). Nephrotoxicity is more prominent in younger age group, in patients receiving higher cumulative doses and in patients who had received cisplatinum prior to alkylating agents (12). Our patient received cyclophosphamide at a cumulative dose of 1022 mg per kg as the sole nephrotoxic chemotherapeutic agent. The evidences of tubular toxicity in our patient are a diminished phosphate reabsorption from the proximal tubules and presence of hypophosphatemic state, proteinuria and hypokalemia. Tubular abnormalities are often reversible but may precede renal insufficiency in drug induced tubular damage (10). The spectrum of renal disease ranges from subclinical and biochemical evidence of renal dysfunction to irreversible renal damage (10). The final serum electrolyte levels of our patient are normal but he has persistent proteinuria that is tubular in origin.

DMSA scan can also be used in the diagnosis of drug induced nephrotoxicity (13). Limited number of studies have shown that 99mTc-DMSA is a reliable indicator of renal function in cisplatinum, and aminoglycoside induced nephrotoxicity and ifosfamide induced tubular injury (14-17). It has been shown that DMSA scan is able to detect subclinical injury (17). A quantitative serial study in children receiving alkylating agents documented a cumulative pattern of injury (18). This pattern showed decreased renal background activity with increased bladder activity. The second DMSA scan of our patient displayed decreased total DMSA uptake of the kidney with increased accumulation in ileocolonic conduit. This scintigraphic pattern can be observed in chronic parenchymal changes, nephrotoxicity, proximal tubular damage such as Fanconi syndrome, or drug interactions affecting protein binding of Tc-99m DMSA (18). The main difference between scintigraphic patterns in chronic parenchymal loss and nephrotoxicity seems that increased liver and spleen activity is not observed in the latter. The higher serum creatinine levels in our patient also support decreased renal uptake of DMSA due to nephrotoxicity rather than drug interactions.

In conclusion, medical team of a cancer patient should keep in mind that tumors of genitourinary tract may present with acute renal failure and may progress to chronic renal failure due to various etiological factors. Chemotherapeutic agents, nephrotoxic antiinfective drugs, breakthrough urinary tract infections, prerenal triggers of renal functions like dehydration, cardiac failure are all potential nephrotoxic factors that should be kept in mind during the treatment of an oncological patient. Close nephrourological follow-up of renal functions, urinary tract infections, hydrenephrosis, continence and adequate reservoir capacity and regular emptying of the reservoir are necessary for the identification of possible late complications, supportive treatment and preservation of renal functions. For such patients, medical team of a cancer patient should also include a pediatric nephrologist who will work in close contact with pediatric oncologist, pediatric surgeon and radiologist.

References


