BK virus associated pronounced hemorrhagic cystoureteritis after bone marrow transplantation

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Ureteral stenosis due to reactivation of the BK virus (BKV) in a state of immunodeficiency is very rare. More common is the appearance of a hemorrhagic cystitis. This report not only shows bilateral ureteral stenosis after bone marrow transplantation, but also presents severe complications as chronic pelvic pain and impaired kidney function as well as irreparable damage to the whole urinary tract leading to nephroureterectomy, subtrigonal cystectomy and orthotopic ileal neobladder. Finally renal transplantation was required. To our knowledge this is the first case in the literature where such a severe course of BKV associated hemorrhagic cystoureteritis is described.

Key Words: BK virus, hemorrhagic cystitis, bilateral nephroureterectomy

Introduction

Although the BK virus (BKV) is widespread with a seroprevalence of up to 90% in the population,[1] it is still not completely understood.[2] Due to a state of immunodeficiency the virus can become reactivated from its latent state residing in the urothelial cell[2] and can cause hemorrhagic cystitis.[2,3] The incidence of BKV associated hemorrhagic cystitis following bone marrow transplantation varies enormously in the literature and lies between 6.5% and 52%.[4,5] BKV also can cause interstitial tubulonephritis, renal failure and ureteral stenosis.[1] There are no reliable data about the frequency of these rare complications occurring after bone marrow transplantation. There is just one case report to be found that describes ureteral stenosis associated with BK virus,[6] where the ureteral stents could be removed after 9 months as the inflammation and the stenosis showed regression. The following case report presents the first case in the literature to our knowledge, where the ureters, the bladder and even the kidneys suffer irreparable damage from BK virus reactivation after bone marrow transplantation, requiring complete removal of the urothelium in the upper urinary tract, cystectomy, orthotopic neobladder and renal transplantation.

Case report

A 9-year-old girl was diagnosed with acute myelocytic leukemia in October 1998. After chemotherapy according to AML-BFM-98 she experienced a relapse in February 2002. She was treated with Imatinib and an HLA-identical allogenic bone marrow transplantation (non-related donor) in June 2002, which resulted in

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a molecular and cytogenetic remission. Two weeks after transplantation a cutaneous graft-versus-host-disease II° was diagnosed. Another 2 weeks later she developed a pronounced hemorrhagic cystoureteritis that was found to be associated with the BK virus. Sonographic examination showed bilateral hydronephrosis. She underwent cystoscopy and retrograde ureteropyelography, which revealed high level strictures on both ureters which made stenting with pigtail catheters necessary. She developed in April 2003 an intestinal graft-versus-host-disease III°. Recurrent bacterial and C. albicans urinary tract infections occurred which made numerous antibiotic and antifungal treatments necessary. The patient suffered from chronic pelvic pain, pollakiuria and dysuria. The pigtail catheters have been changed periodically, but due to the persistent stricture and insufficient drainage they could not have been removed. In this young patient bilateral percutaneous nephrostomies were not the preferred solution, in plus the attempt to remove the pigtail catheters failed. The pain and the dysuria persisted after the antimicrobial treatment, so that instillations with triamcinolone acetonide and mepivacaine were performed, with initially fair, but then decreasing success. The bladder took damage too, as it developed into a contracted bladder. After failure of the instillation treatment, intra-detrusor botox injections have been performed, but they failed to achieve a sufficient long term result too. Due to the recurrent urinary tract infections, the chronic hydronephrosis and a secondary focal segmental glomerulosclerosis the kidney function was increasingly impaired. Also the insertion of a Memokath ureteral stent did not stabilize the renal function. After having reached a glomerular filtration rate of 26 mL/min, renal scintigraphy showed a relative function of the left kidney of only 24%. Based on these findings, we decided to perform a nephroureterectomy of the left kidney, a ureterectomy of the right ureter with subtrigonal cystectomy and orthotopic ileal neobladder that was connected by an afferent loop for ureteral replacement to the right renal pelvis, Figure 1. The aim of this surgery, which took place in September 2010, was to repair the bilateral ureteral strictures, increase the bladder capacity and create a continent urinary system with no foreign bodies (ureteral catheters and stents) to minimize the infection risk, also regarding a possible renal transplantation that could become necessary. Pelvic pain and discomfort during voiding disappeared after bladder substitution with the orthotopic neobladder, Figure 2. Just 4 weeks after that complex surgery, the meanwhile 21-year-old patient presented with uremia

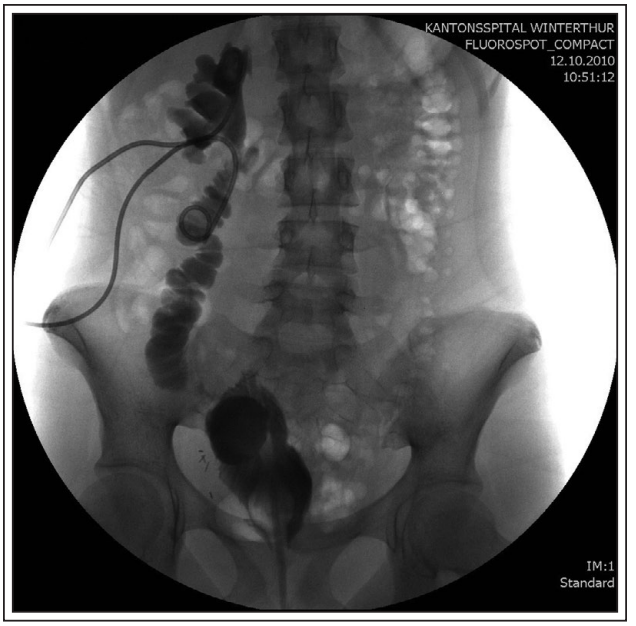

Figure 1. Postoperative contrast imaging of the orthotopic ileal neobladder with the afferent loop to the right renal pelvis.

(creatinine 620 µmol/L), metabolic acidosis (pH 7.0, BE -19.2) and renal anemia (Hb: 7.2 g/dL) so that hemodialysis and administration of erythropoietin was required. Regarding the patient's history the renal insufficiency that did not recover was considered as multifactorial, but largely associated with the

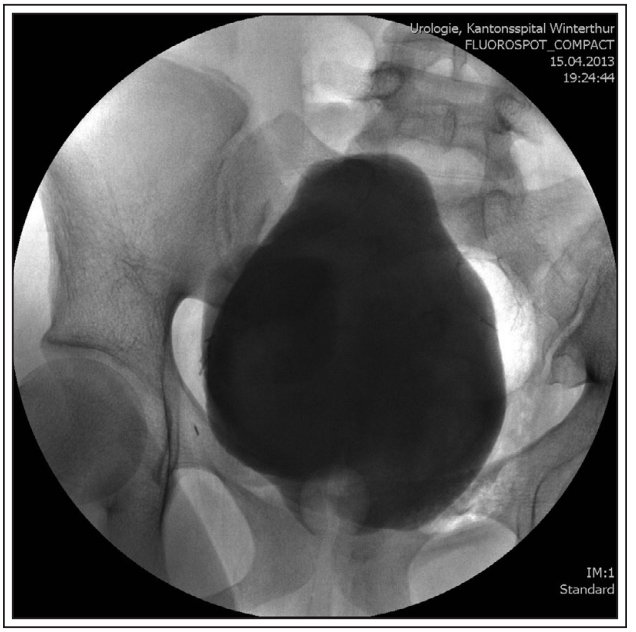

Figure 2. Ileal neobladder with sufficient capacity and no reflux.

reactivated BKV after the bone marrow transplantation in 2002. To remove most remaining urothelial tissue, and so creating best possible conditions in order to avoid a BKV associated nephropathy of the allograft, we decided to perform a nephroneoureterectomy of the remaining right kidney, which took place in March 2011. Further immunohistochemistry analysis with SV-40 did not detect BKV in either kidney. Simultaneously a renal transplantation was planned with donor-nephrectomy from the patient's 50-year-old father. Meanwhile hemodialysis was continued every second day. The uneventful living-donor transplantation followed in May 2011. The patient could be discharged with a sufficient glomerular filtration rate of 52 mL/min. In September 2011 the patient presented with elevated creatinine. Sonography showed transplant hydronephrosis I°. Due to failure of retrograde catheterization of the ureter, an antegrade pigtail catheterization was performed after dilatation of the ureteral stenosis with the Uromax balloon system. The pigtail catheter could successfully be removed 5 months later. Due to post void residual urine of 200 mL intermittent self-catheterization became necessary to protect transplant function, which the patient performed without difficulty. The patient describes her quality of life as good. She could start working again part-time as she got no pain or discomfort and no urinary tract infections since the cystectomy took place. Also the transplant function remained stable.

Discussion

Most cases of hemorrhagic cystitis associated with BK virus can be treated with supportive measures such as hyperhydration and forced diuresis whereas severe cases may need bladder irrigation or even a surgical approach in the case of strong macrohematuria with clots.[3,7] BK virus associated ureteral stenosis were often described in connection with renal transplantation,[1,8] but only one report by Gaston presented BKV ureteral stenosis after bone marrow transplantation.[6] A graft versus host disease (gvhd) was shown as the most important risk factor for the development of a hemorrhagic cystitis after bone marrow transplantation;[9] our patient suffered just 2 weeks before the hemorrhagic cystitis manifestation of a gvhd. Nevertheless a clinical course as described that resulted in a complete decompensation of the urinary tract with a complex and extensive treatment can be considered as a rarity. To our knowledge this is the first case in the literature where bilateral nephroureterctomy, cystectomy, ileum-neobladder and renal transplantation was necessary after a pronounced hemorrhagic cystoureteritis associated with BK virus after bone marrow transplantation. Furthermore, the case proves the technical and functional feasibility of a renal transplantation after upper urinary tract diversion with an orthotopic ileal neobladder. Despite the long term ureteral stenting for 8 years, the kidney function could not been preserved. It is difficult to differ what affected the renal function most. The combination of BKV, the chronic hydronephrosis and the secondary focal segmental glomerulosclerosis eventually lead into renal insufficiency. The aim of our extensive surgical treatment was to regain quality of life for that young patient with chronic pelvic pain, pollakiurie and dysuria due to infection, bilateral ureteral stenting and a contracted bladder. These problems could be solved with the subtrigonal cystectomy and orthotopic ileal neobladder. Unfortunately shortly after this surgery renal function worsened and hemodialysis was required. As an improvement of the renal function of the remaining kidney was very unlikely, we decided to perform the renal transplantation to achieve the most possible quality of life without dialysis. □

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