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Case Report

A rare urinary JC virus reactivation after long-term therapy with rituximab

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ABSTRACT

The possible role of JC virus in determining urinary tract involvement has only recently been recognized. The case of a man with laboratory-confirmed JC virus replication in the urine after a maintenance schedule of rituximab administered for a lymphoproliferative disorder is reported herein. The patient developed severe renal and urinary tract impairment, characterized by the onset of nephropathy, bilateral ureteral strictures, and a serious reduction in vesical compliance, ultimately requiring an ileal neobladder configuration. The renal and urinary tract involvement was finally attributed to JC virus reactivation. This observation suggests that renal and urinary tract diseases related to JC virus might be associated with long-term rituximab treatment.

Introduction

BK and JC viruses are human polyomaviruses infecting most people throughout the world, as shown by the presence of antibodies against viral proteins in about 80% of the human population (Pinto and Dobson, 2014). These viruses have been shown to establish latency in several tissues including the urinary system. In renal transplant patients and more generally in those suffering from immune system impairments, human polyomaviruses can on rare occasions cause tubulo-interstitial nephritis (Boldorini et al., 2005; Kantarci et al., 2011). Nevertheless, data regarding the ability of JC virus to induce ureteral and bladder damage are very scarce (García Ligero et al., 2002; Cavallo et al., 2007).

The triggering mechanisms for JC virus reactivation are not well defined yet. It has recently been suggested that there is a higher risk of JC virus reactivation in immunocompromised patients and those treated with immunomodulatory drugs for chronic inflammatory disorders, haematological malignancies, or following organ transplantation (Kartau et al., 2019). However, drug-specific causality is difficult to assess, since most patients receive multiple immunomodulatory medications concomitantly or sequentially, or present with several immunocompromising factors related to their underlying disease. At the level of the urinary tract, the association between patient immune status and JC virus pathogenicity appears even more ambiguous, due to the limited available evidence. Moreover, low levels of JC viruria can also occur in approximately 13–20% of healthy individuals (Boukoum et al., 2016; Markowitz et al., 1993), making the interpretation of data even more difficult.

This article presents an uncommon case of JC virus reactivation determining urogenital involvement in a patient with a diagnosis of CD-20-expressing B-cell non-Hodgkin lymphoma treated with rituximab.

Case presentation

A 55-year-old man, suffering from chronic kidney disease and treated with chemotherapy 20 years previously due to evidence of a follicular lymphoma, underwent a robot-assisted radical prostatectomy and extended lymph node dissection in March 2015 for high-risk prostate cancer. The final histopathological

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examination revealed the presence of acinar-type prostatic adenocarcinoma, Gleason score 4 + 5 = 9, with extraprostatic extension, involving the left seminal vesicle (American Joint Committee on Cancer (AJCC) pT3b). The 38 lymph nodes removed were found to be free from prostatic tumour involvement; however follicular lymphoma with a nodular pattern (CD20+, CD10+, BCL6+, BCL2+, MIB1 20–30%) was detected at this level. As a result, systemic chemotherapy with six cycles of R-bendamustine plus maintenance with 3-monthly rituximab therapy for 2 years was administered.

In April 2018, the patient started complaining of lower abdominal pain associated with gross haematuria, dysuria, and occasional fever. Urinary cytology was negative and ultrasonography of the abdomen showed thickened vesical walls without any papillary lesion detectable. As a result, in May 2018 he underwent bladder mapping with multiple transurethral biopsies, revealing the presence of an extensive bladder inflammatory lymphomonocytic infiltrate without histological evidence of any vesical malignancy. Assuming a case of chemical cystitis, endovesical therapy with six weekly mesna instillations was administered, however without any benefit.

In August 2018, the patient presented once again with gross haematuria and fever up to 39 °C, requiring hospitalization. Blood samples revealed a haemoglobin level of 9.9 g/dl, white blood cell count of 9.94 × 10^9/l, C-reactive protein of 137 mg/l, and procalcitonin of 0.22 ng/ml. The leucocyte formula was within normal limits, with 67% neutrophils and 14% lymphocytes. Blood cultures were negative, while a serum proteinogram demonstrated mild hypogammaglobulinemia. Total IgG, IgM, and IgA serum levels were 4.47, 0.29, and 0.17 g/l, respectively. Urinalysis revealed urine pH 6.5, haemoglobin 0.03 mg/dl, and leukocyte esterase 500 mg/dl, while the presence of nitrites was not detected. Urinary sediment analysis revealed 2074 white blood cells/μl and 134 red blood cells/μl. A bladder catheter was placed and empirical antibiotic therapy with intravenous piperacillin–tazobactam 4 g + 500 mg every 8 h was started.

Ultrasonography of the abdomen showed bilateral grade 2 hydronephrosis, while concurrent blood chemistry tests revealed a progressive worsening of renal function indices, with serum creatinine rising up to 4.8 mg/dl. As a consequence, the patient underwent a bilateral percutaneous nephrostomy placement. After serum creatinine recovery, a contrast-enhanced abdominal computed tomography scan and bilateral pyelography were performed, revealing multiple bilateral lumbar ureteral stenoses (Figure 1A). Quantitative real-time PCR (RT-PCR) was used to search for BK and JC viruria, detecting 3442 copies/mL of JC virus DNA in the urine. Urine culture revealed the concomitant presence of extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli*. Cranial magnetic resonance imaging (MRI) was performed in order to exclude progressive multifocal leukoencephalopathy (PML). The patient was negative for antibodies to HIV-1 and HIV-2. Multiple urine samples were negative for mycobacteria by culture. The PCR fragments from urine samples were sequenced and analysed. The sequence of the non-coding control region (NCCR) was identical to the archetype except for two point mutations, A39T and C259A.

Oral therapy with mirtazapine 100 mg/day and intravenous linezolid 600 mg every 12 h plus meropenem 1 g every 8 h was administered, with complete resolution of the fever and progressive normalization of the inflammation indices. A simultaneous immunoglobulin infusion was provided to correct the hypogammaglobulinemia. After nearly 1 month of hospitalization, the patient was discharged with indwelling bilateral nephrostomies and a bladder catheter. Retrograde cystography showed an extreme reduction of bladder capacity, equivalent to nearly 20 ml (Figure 1B).

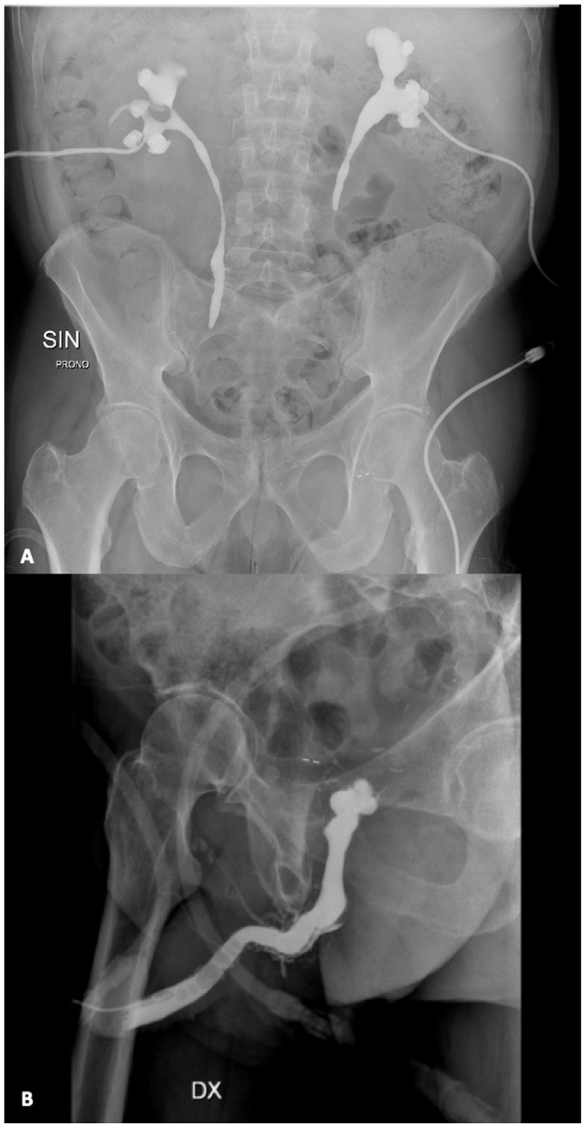

Figure 1. (A) Bilateral pyelography showing multiple bilateral lumbar ureteral stenoses ultimately preventing contrast medium passage. (B) Retrograde cystography showing an extreme reduction of bladder capacity. The maximum tolerated filling volume was equal to nearly 20 ml.

As a result, in July 2019, the patient underwent a totally intracorporeal robotic ileal Y-shaped neobladder reconfiguration. On day 10 postoperative, the patient was discharged with bilateral ureteral splints and a urinary catheter. The ureteral splints were removed on days 12 and 14 postoperative, respectively, while the bladder catheter was removed 21 days after the intervention. At the 3-month follow-up, ^{123}I-hippuran sequential renal scintigraphy showed no signs of urinary obstruction; the right parenchymal mean transit time was within normal limits, while it was slightly reduced on the left. At the 1-year follow-up, the last serum creatinine level was 3.1 mg/dl. The renal and urinary tract involvement was finally attributed to JC virus reactivation.

Discussion

This paper aims to highlight an unusual case of severe urinary tract impairment possibly secondary to JC virus reactivation after rituximab therapy. JC virus is a member of the polyomavirus family, mainly known as the etiological agent of PML. The central nervous system and kidney are considered as the reservoirs of JC virus infection, in which

the virus can persist in latency after primary infection (Boldorini et al., 2005). The possible role of JC virus in determining urinary tract involvement has only recently been recognized. Based on laboratory findings and PCR studies, several authors have long considered BK virus as the only polyomavirus eventually affecting the kidneys and urinary tract. Indeed, although genomic sequences of both JC virus and BK virus DNA have been detected by PCR in renal biopsies of transplanted patients, combined immunohistochemical and molecular biology studies suggested that renal impairment was secondary to the replication of BK virus, whereas JC virus was usually present as a co-infecting agent in a latent, non-replicative phase (Boldorini et al., 2001). As such, JC virus has long been considered unable to elicit pathological effects.

Nickeleit et al. (2000) proposed that JC viral particles produced after a viral lytic cycle in the renal pelvis or ureter may enter the capillary vessels and infect the tubular cells of the kidney or, alternatively, follow an ascending route of infection from transitional cells to kidney tubular cells. Conversely, Boldorini et al. (2003) first reported morphological evidence of lytic JC virus infection in four renal specimens from AIDS patients, supporting the hypothesis that, in immunocompromised patients, active JC viral replication can also occur in the kidney and urinary tract. JC virus-related nephropathy is now recognized as a rare cause of nephropathy in transplant recipients (Wiegley et al., 2020). Ureteral and bladder involvement is more rarely reported in different types of immunosuppressed patients (García Ligero et al., 2002; Cavallo et al., 2007).

Genomic rearrangements of archetypal regulatory regions in the JC virus genome regulating viral latency and replication may favour viral reactivation and the development of symptoms. Indeed, the JC virus genome contains a hypervariable NCCR, which controls early and late gene transcription and DNA replication. Several conditions such as immunosuppression or modifications in the tissue microenvironment (i.e., those occurring in patients who have undergone kidney transplantation) have been suggested as a possible trigger for genomic instability and JC virus reactivation. However, it is still debated whether NCCR rearrangements could play a significant role at the level of the kidneys and urinary tract.

Consistent with the current literature, we found an archetype JC virus strain in the urine. Similarly, Seppälä et al. (2017) showed only archetype NCCR being present in one patient with JC virus-associated nephropathy and in multiple kidney transplant recipients. It seems that rearrangements within the NCCR region are more prevalent in PML patients, thus indicating an adaptation process leading to more active virus variants with altered tissue tropism.

It appears that there are no published data concerning JC virus urinary reactivation in patients being treated with rituximab. Actually, a higher incidence of infections has been reported in patients with lymphoproliferative disorders receiving rituximab, although clinical trials have shown conflicting results. Recent evidence suggests that, in addition to its effect on B-cells, rituximab might influence T-cell immunity, ultimately predisposing the patient to viral and opportunistic infections (Kelesidis et al., 2011). Furthermore, apart from their role in antibody synthesis, B-cells may also act as antigen-presenting cells. In this light, rituximab may dysregulate cofactors involved in an effective immune response. Moreover, rituximab might be able to induce immunosuppression through several other mechanisms such as delayed-onset neutropenia and hypogammaglobulinemia, especially when administered for long periods (Lim et al., 2008). In the case presented herein, it appears reasonable that rituximab might have contributed to JC virus reactivation, although no definite conclusions can be drawn.

As a main limitation, we acknowledge that we could not ascribe the clinical presentation to JC virus reactivation with absolute certainty, since JC virus urinary shedding can also occur in a small percentage of healthy individuals, albeit with lower viral loads. Further studies are warranted to investigate JC virus-mediated nephropathy and uropathy in immunocompromised, non-transplanted patients.

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Ethics statement

The patient gave his written informed consent to publish this case report, including the images of the studies performed. All procedures conducted in this study involving human participants were performed in accordance with the ethical standards of the institutional and national research committees and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Conflict of interest

All authors disclose no financial or personal relationships with other people or organizations that could inappropriately have influenced their work.

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