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Prikaz bolesnika | Case report

Renal Failure Associated with Human Polyomavirus BK and Human Adenovirus in a Child with Acute Lymphoblastic Leukaemia

Zatajenje bubrega povezano s humanim BK poliomavirusom i humanim adenovirusom u djeteta s akutnom limfoblastičnom leukemijom

Vedran Stevanović[1], Matej Jelić[2], Maja Pavlović[2], Ernest Bilić[2,3], Goran Tešović[1,3]

[1] Pediatric Infectious Diseases Department, University Hospital for Infectious Diseases „Dr Fran Mihaljević", Mirogojska 8, 10000, Zagreb, Croatia
[2] Department of Paediatrics, University Hospital Centre Zagreb, Kišpatićeva 12, 10000, Zagreb, Croatia
[3] School of Medicine, University of Zagreb, Šalata 3, 10000, Zagreb, Croatia

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✉ **Corresponding author:**
Vedran Stevanović,
University Hospital for Infectious Diseases „Dr Fran Mihaljevic", Pediatric Infectious Diseases Department, Mirogojska 8, 10000 Zagreb, Croatia;
E-mail: vedran.stevanovic@gmail.com

Alternate author:
Matej Jelić,
University Hospital Centre Zagreb, Department of Pediatrics, Kispaticeva 12, 10000 Zagreb, Croatia;
E-mail: matejjelic1@gmail.com

Abstract

Immunocompromised patients are susceptible to multiple severe viral infections. This paper describes a 4-year-old boy with newly diagnosed B-cell precursor acute lymphoblastic leukaemia. The 4-year-old patient developed haemorrhagic cystitis, obstructive nephropathy and renal failure due to human polyomavirus BK and human adenovirus co-infection. Cidofovir should be used only in life-threatening cases.

Sažetak

Imunokompromitirani su bolesnici podložni višestrukim teškim virusnim infekcijama. U radu opisujemo četverogodišnjeg dječaka s novodijagnosticiranom prekursorskom B-staničnom akutnom limfoblastičnom leukemijom koji je razvio hemoragijski cistitis, opstruktivnu nefropatiju i zatajenje bubrega nakon ko-infekcije humanim BK poliomavirusom i humanim adenovirusom. Cidofovir treba primjenjivati samo u slučajevima u kojima postoji životna opasnost.

Introduction

Immunocompromised patients are susceptible to multiple severe viral infections. In patients with haematologic malignancies, a lack of immunological competence caused by chemotherapy and conditioning procedures results in lymphopenia[1]. Patients with lymphopenia are at increased risk to develop primary or reactivate latent viral infection. One of the infections due to lymphopenia can be haemorrhagic cystitis (HC). The most common infectious causes of HC are human polyomavirus BK (HPyVBK) and human adenovirus (HAdv). Other causes of HC are presented in Table 1[2].

Most primary infections with HPyVBK occur at a young age (approximately 50-90% are seropositive by 10 years of age) and are either asymptomatic or associated with fever and upper respiratory tract symptoms [3,4]. Following primary infection, the virus establishes latency, especially in the tubular cells of the kidney. Approximately 7% of healthy individuals have per-

sistent HPyVBK viruria[3]. In immunocompromised patients, HPyVBK is frequently reactivated, thereby causing inflammation of the urinary tract and the kidneys in particular[3,4].

More than 80% of diagnosed HAdv infections occur in children < 4 years old[5]. Asymptomatic carriage of HAdv may persist for months. Latent HAdv may be found in lymphoid tissue, renal parenchyma or other tissues for years and reactivation may occur in severely immunosuppressed patients[3,5]. Although HAdv infections in immunocompetent individuals may be asymptomatic and are self-limiting, the immunocompromised patients may present with a broad spectrum of clinical manifestations[1,5]. Most common serotypes associated with HC include HAdv-11, -34, -35, -3, -7 and -21[5].

Clinical manifestations of viral HC include dysuria, low abdominal pain and a variable degree of haematuria. Although viral HC caused by HPyVBK or HAdv is self-limiting in immunocompetent patient, in immunocompromised it can be severe[3,4,5]. Furthermore, HC is classified into 4 grades: grade 0: no haematuria, grade I: microscopic haematuria, grade II: macroscopic haematuria, grade III: haematuria with blood clots, and grade IV: haematuria and blood clots resulting in obstructive uropathy[3]. The pain can be severe and haematuria can be extensive resulting in anaemia requiring blood transfusions. Blood clotting may also occur and result in urinary tract obstruction, which in turn can lead to secondary renal failure[4]. However, fatal or dialysis-dependent renal failure is quite rare[5]. The aim of our study is to increase the awareness and emphasize the rare complications of viral HC in children with haematologic malignancies.

Case Report

A 4-year-old boy presented with a fever of 38.8°C lasting for four days. He had no other symptoms, but his parents noticed that he started to get more tired and slept more frequently within a month. He had no weight loss. Upon physical examination, only slightly enlarged lymph nodes of the neck were remarkable. Initial laboratory findings included haemoglobin of 72 g/L, WBC of 1.8 x 10^9/L, thrombocytes of 65 x 10^9/L with liver enzymes and lactate dehydrogenase within normal range. Urine analysis results were normal.
Registered pancytopenia raised a suspicion of a hematologic malignancy and bone marrow aspiration (BMA) was indicated. Bone marrow cytology and immunophenotyping proved precursor B-cell acute lymphoblastic leukaemia (pre B-ALL) with 60% aberrant B-cells while cytogenetic results showed tetrasomy 21 and trisomy 14 and 22.

Induction chemotherapy was initiated according to ALL IC-BFM 2009-IA protocol. Initial treatment response was very good and he was classified in standard risk group. On day 31, complete blood count included WBC of 2.0 x 10^9/L and relative lymphocyte count of 10%. On day 36 of hospital stay, before continuation of treatment (IB protocol which is started with cyclophosphamide), the patient developed macrohematuria, elevated serum creatinine to 134 μmol/L and within 24h he had no urine output. He was transferred to the PICU department with acute kidney injury stage III and haemodialysis was initiated. Renal ultrasound (RUS) revealed hyperechogenic mass of 9 mm in the bladder, believed to be a blood clot, and bilateral proximal dilatation of the renal collecting system as well as both kidneys classified as hydronephrosis grade I./II. Abdominal ultrasound revealed fatty liver with no other irregularities. CT urogram revealed hyperdense masses in both ureters and bladder, possible blood clots, with bilateral dilatation of the renal collecting system.

Urine culture was non-specific and urine real-time polymerase chain reaction (PCR) for HPyVBK, as well as urine real-time PCR for HAdv, turned out to be positive. Quantitative detection by real-time PCR showed 226000 copies/mL of HPyVBK and >1000000 copies/mL of HAdv, appointing to viral HC caused by co-infection of HPyVBK and HAdv.

Within three days at PICU, the patient's condition improved and he started having normal urine output upon supportive treatment. Diuretics were not used. On day 41, RUS revealed mild proximal dilatation of the renal structures and no more visible masses. Serum creatinine dropped to 16 μmol/L, so haemodialysis was discontinued and further diagnostic and treatment modalities for leukaemia were continued.

Discussion

Viral co-infections occur in a substantial number of children with impaired immunity. Simultaneous infections of HAdv and HPyVBK, human cytomegalovirus, Epstein–Barr virus or respiratory syncytial virus have been described in patients with haematological malignancies[1]. However, most of the cases related to HC caused by HPyVBK, HAdv or both are described in patients undergoing haematopoietic stem cell transplantation (HSCT), not in healthy individuals or other immunocompromised patients[3,6,7]. When described in other immunocompromised patients, HC is often explained as a drug-induced complication following the conditioning regimen, usually cyclophosphamide-induced when it occurs early after HSCT [3,7,8]. Even more, in HSCT patients, HPyVBK viruria is ex-

pected in up to 100% cases, while HC develops in 16-62% of HSCT recipients when HAdv is the cause in 10-77% of those cases[3].

Montaruli et al. described a case of adenovirus-induced obstructive uropathy with acute renal failure in a 14-year old boy, but he already received cyclophosphamide for his refractory pre B-ALL[8]. Although our patient had newly diagnosed pre B-ALL, he developed HC grade IV and acute kidney injury before his scheduled use of cyclophosphamide. Cyclophosphamide was delayed. Therefore, our patient received it at the end of the protocol, after recovery from the HC and renal failure. He had no side effects after cyclophosphamide in terms of HC.

Whereas our patient had a significant number of viral copies in his urine, it is hard to conclude which virus was the predominant cause of HC and renal failure. Interestingly, Bil-Lula et al. described enhanced replication of HAdv in the presence of HPyVBK which may lead to increased virulence in HAdv infections and serious consequences in immunocompromised patients [1]. As our patient was only 4-years old, it is hard to conclude whether he developed primary infection or a latent one has been reactivated due to immunosuppression. Furthermore, nosocomial transmission of both HPyVBK and HAdv has been described[3].

The diagnosis of HPyVBK or HAdv caused HC may be confirmed by PCR in urine[4,5]. Moreover, the treatment for HPyVBK infection is symptomatic with forced diuresis and analgesics. Treatment of HAdv infection is supportive, however, specific antiviral therapy against HAdv exists in a form of cidofovir.

Cidofovir is a nucleoside phosphonate analogue that decreases viral DNA synthesis. The major adverse effect of cidofovir is nephrotoxicity. In immunocompromised children, cidofovir appears to be safe in a single dose for life-threatening viral infections, despite chemotherapy and other administered nephrotoxic agents [9]. Our patient did not receive cidofovir due to the rapid recovery upon supportive treatment.

In conclusion, we described a 4-year old boy with newly diagnosed pre B-ALL who developed dialysis-dependent renal failure due to HPyVBK and HAdv co-infection. Since both HPyVBK and HAdv are capable to enter long term latency following primary infection and both are very common in immunocompromised patients, their co-infection should always be considered as undesirable and likely to worsen the clinical course and outcome. Renal complications are rare and characterized by obstructive uropathy and renal failure. The diagnosis can be made by urine PCR analysis without invasive intervention, such as kidney biopsy. Cidofovir should be used only in life-threatening cases.

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