BK Virus Associated Late Onset Haemorrhagic Cystitis After Allogeneic Peripheral Blood Stem Cell Transplant

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Abstract Haemorrhagic cystitis (HC) after allogeneic stem cell transplant is a clinical disorder with multiple etiologies. There is an inflammation of the bladder mucosa leading to painful haematuria. Early onset HC is mainly attributed to conditioning chemotherapy consisting of cyclophosphamide. Late onset HC is now being related to reactivation of latent polyoma BK virus (BKV). We describe the case of a 37 year old male with acute myeloid leukemia presenting with haematuria after allogeneic stem cell transplant.

Keywords BK virus · Decoy cell · Stem cell transplant

Introduction

Polyoma BK virus (BKV) is a non-enveloped DNA virus containing a 5 kb circular double stranded DNA [1]. The association between late onset haemorrhagic cystitis (HC) and BKV was initially described in 1971 [2]. Primary infection occurs during childhood which manifests as mild “flu-like illness” [3]. Subsequently the virus becomes latent and reactivation occurs in conditions causing severe immunosuppression e.g. haemopoietic stem cell transplant [4].

BKV has been associated with nephropathy in patients receiving renal transplant but the presence of BK viruria

has long been associated with painful haematuria in patients undergoing allogeneic stem cell transplant [5]. HC is a common complication following stem cell transplant. Its frequency varies from 7 to 68%. HC is classified into two types: Early onset, occurring within 48–72 h, generally due to the toxic effects of the conditioning regimen including cyclophosphamide; and late-onset, occurring after 72 h with pathogenesis related to multiple etiologies—BKV infection being one of them [6] (Figs. 1, 2).

Diagnosis of BKV infection requires the presence of Decoy cells (DCs) in urine sediment. DCs are BKV infected cells shed into the urine from renal tubules and urothelium. They are identified by their typical intranuclear viral inclusion and their detection in the urine from transplant recipients assesses the risk for BKV associated nephropathy [7]. Herein we describe a case of 37 year male with acute myeloid leukemia who presented with haematuria at day+80 post transplant. Urine cytospin showed presence of DCs which were suggestive of BKV associated nephropathy.

Case Report

A 37 year old male, doctor by profession was diagnosed as a case of acute myeloid leukemia in September 2009. He received induction with daunorubin and cytosine (3 + 7 regimen) followed by four cycles of consolidation with high dose cytosine arabinoside which were completed in March 2010. A decision was taken for allogeneic BMT in October 2010 since he had a HLA matched sibling donor. Conditioning was given with busulfan 4 mg/kg/day for 4 days and cyclophosphamide 60 mg/kg/day for 2 days. During the myelosuppressive phase he required multiple blood ± blood product support along with intravenous

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Fig. 1 Urine cytospin containing BKV cells at 20x

Fig. 2 Single decoy cell at 40x

antibiotics and total parenteral nutrition. He engrafted on day+9 and was discharged from the transplant unit with growth factor and blood transfusion independency. Complete blood counts on the day of discharge (day+19) were Hb: 9.5 g/dl, Hct: 27.0%, WBC: $4.1 \times 10^9/l$ and platelets: $72 \times 10^9/l$.

On day+26 he developed nausea and vomiting. On examination he had mild abdominal discomfort. Complete blood counts showed Hb: 11.8 g/dl, Hct: 33.2%, WBC: $8.8 \times 10^9/l$ and platelets: $41 \times 10^9/l$. Cytomegalovirus PCR studies were negative however, antral and duodenal biopsies showed occasional apoptotic bodies. Although the features were subtle, patient was started on steroids (methylprednisolone pulse for 5 days followed by oral prednisolone). His symptoms improved. Hence, prednisolone was tapered off and discontinued. On day+50 during his routine follow-up visit, he complained of itching all over the body. Features of skin biopsy were compatible with graft versus host disease (late scleroderma type). At this point prednisolone was restarted at a dose of 30 mg $\times$ twice daily.

On day+80 he presented with complaints of gross haematuria. Complete blood counts showed Hb: 12.6 g/dl, Hct: 36.6%, WBC: $7.8 \times 10^9/l$ and platelets: $45 \times 10^9/l$. Coagulation profile (PT/APTT) was normal. Serum creatinine was 1.1 mg/dl. Total bilirubin was 1.9 mg/dl; indirect bilirubin was 1.3 mg/dl. Urine detailed report revealed hemoglobin: large (3+), nitrites: negative, red blood cells more than 20/high power field and leukocytes 10/high power field. A suspicion of cyclophosphamide induced or polyoma virus associated HC was made and a urine cytospin was ordered. The smear showed DCs exhibiting nuclear enlargement, hyperchromasia with smudgy chromatin and homogenous nuclear inclusions. Microscopy was suggestive of polyoma BKV infection.

Other investigations included bone marrow trephine which showed acute myeloid leukemia in haematological remission. Chimerism studies of short tandem repeats analysis using PCR with fluorescent primers and capillary electrophoresis was also performed and donor chimerism was more than 95%.

Patient was treated with intravenous hydration and continuous bladder irrigation for 4 days. On the fifth day, the number of red blood cells/high power field in urine sample decreased. On the seventh day of treatment urine microscopy was completely clear of red blood cells. He was discharged the following day.

Discussion

The link between polyoma BKV and HC was first suggested in 1976 when papovaviruses like particles were found in the urine of patients with gross haematuria [8]. BKV is a ubiquitous organism which causes sub clinical infection within the first 10–15 years of life [9]. After the primary infection has occurred latency is established in renal tissues and circulating B lymphocytes [10]. BKV nephropathy and graft dysfunction is a significant problem in solid organ transplantation and has been well documented in pancreas–kidney recipients [11]. Late onset HC in recipients of stem cell transplant is generally associated with a viral infection and polyoma BKV and cytomegalovirus are the most common pathogens implicated [12]. Vidas et al. [13] showed 100% sensitivity, 100% negative predictive value and 6% positive value of finding urinary DCs in BK nephropathy. However, DCs are not exclusive for BKV. They may be present in other viral infections due to JC polyomavirus and cytomegalovirus. In our case CMV was ruled out as PCR studies were negative.

The use of potent immunosuppressive drugs, particularly in the last decade, to prevent graft rejection has made reactivation of latent infection by BKV relatively common [14]. Our patient was on oral cyclosporine (4 mg/kg/day)

when he developed haematuria therefore suppressed immunity could be one causative factor.

Literature review shows that the correlation between HC and graft versus host disease is controversial [15]. While some reports suggest HC as a manifestation of graft versus host disease, many others do not support this issue [16]. In our patient graft versus host disease preceded HC indicating reactivation of the virus from immunosuppression. Haemopoietic reconstitution itself leads to an immunological response to viral antigens expressed on uroepithelium causing mucosal damage and haemorrhage [17].

The limitation of our case report includes the inability to perform histopathology which is a gold standard test for BKV detection [18]. Additional supportive tests include DCs in urine, electron microscopy and quantitative PCR studies [19]. However, the clinical presentation, CMV negativity and presence of DCs on urine microscopy were highly suggestive of BK viremia.

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