SHORT REPORT

BK virus associated haemorrhagic cystitis in related donor haematopoietic stem cell transplant recipients: A developing country experience

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Abstract

A retrospective cross sectional study was conducted at the Virology Department, Armed Forces Institute of Pathology (AFIP) and Armed Forces Bone Marrow Transplant Centre (AFBMTC), Rawalpindi, from January 2016 to July 2018. Medical records of 193 patients were examined to determine the number of patients developing Haemorrhagic Cystitis associated with BK virus (BKV). BKV PCR testing was done on the patients' urine samples. Cytomegalovirus reactivation was also assessed weekly from day 30 to day 100, by CMV quantitative PCR testing on blood samples. Out of 193 patients, 11 (5.6%) developed haemorrhagic cystitis and all these patients were positive for BKV on urine samples. The maximum number of positive cases, i.e. 5 (2.6%) was in the age group three months to 10 years. Primary disease in seven out of 11 cases was Beta-Thalassemia Major.

Keywords: Haemorrhagic cystitis, Haematopoietic stem cell transplant, BK virus.

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Introduction

Haemorrhagic cystitis (HC) is a well-known cause of morbidity and mortality in haematopoietic stem cell transplant (HSCT) recipients. It is characterised by the presence of haematuria and urinary symptoms in patients, after starting the conditioning regimen. Its occurrence ranges from 5%-68% in allogenic stem cell transplant patients.[1,2] Early onset HC is usually due to damage to urothelial mucosa by drugs and radiotherapy, while late onset HC is associated with BK virus (BKV).[3] BKV is a small double stranded DNA virus belonging to the family Polyomaviridae.[4] The virus was first isolated, in 1971, from the urine of a Sudanese renal transplant patient with ureteric stenosis and was named after the patient's initials.[5] In HSCT recipients, HC contributes to prolonged hospital stay and worsening of quality of life.

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In HSCT recipients, BK viruria results in wide variety of presentations including asymptomatic haematuria, haemorrhagic cystitis, ureteral stenosis and interstitial nephritis. Among these, HC is the most common complication with significant morbidity and mortality.[6] Factors predisposing to HC in HSCT include conditioning regimen, advanced age at immunosuppression, graft versus host disease, thrombocytopenia, coagulopathy and other viral infections.[7]

No study has been carried out in the past about BKV associated HC in any bone marrow transplant centre in Pakistan. We conducted a retrospective study on BKV associated HC in HSCT patients in our set up and analysed some of the risk factors associated with this disease. This study will provide an insight to a disease caused by a rare virus in immunocompromised individuals.

Methodology

This retrospective study was conducted at the Armed Forces Institute of Pathology (AFIP), Rawalpindi, between January 2016 and July 2018. The subjects included all patients who underwent HSCT (auto, allo or haplo) during the study period, at the Armed Forces Bone Marrow Transplant Centre (AFBMTC), Rawalpindi, Pakistan. The study was approved by the ethical committee of the institute. Written informed consent was obtained from all the patients or from the parents of the patients in case of minors (less than 18 years of age).

The medical record of 193 patients were examined to determine the number of patients developing HC associated with BKV and the record for potential risk factors such as age, gender, primary disease, prior immunosuppression, HLA matching, number of days after transplant when HC developed, CMV reactivation, GVHD, conditioning regimen and post-transplant immunosuppression and outcome was also obtained. Three millilitres of urine sample of the patients was collected into sterile urine bottles and transported to the virology department. BKV PCR testing (Sacace Biothecnologies, Italy) was done on the urine samples of the patients. CMV reactivation was also assessed in these patients, weekly from day 30 to day 100, by CMV quantitative PCR testing (Sacace Biothecnologies, Italy) on blood samples. Pre-emptive antiviral therapy was

recommended in patients with CMV viraemia of >1000 copies/ml.

Statistical analysis was performed with SPSS 21. Mean and SD was calculated for numerical variables like age, while frequency and percentage was calculated for gender, age groups, HLA matching, CMV reactivation, GVHD, and outcome. Statistical significance was determined at the level of $p<0.05$.

Results

Out of the total 193 patients who underwent HSCT in our setup during the study period, 137 (71%) were males and 56 (29%) were females. The age range was from 3 months to 62 years; mean age was 15.63±14.35 years.

Eleven (5.7%) patients developed haemorrhagic cystitis and all of these 11 (100%) symptomatic patients had positive PCR result for BKV virus on urine sample.

Table-1: Age distribution of patients undergone HSCT.

Age groups	BKV Negative	BKV Positive	Total	
3mo-10yrs	95(49.2%)	5(2.6%)	100(51.8%)	
11-20yrs	34(17.6%)	4(2.1%)	38(19.7%)	
21-30yrs	28(14.5%)	1(0.5%)	29(15%)	
31-40yrs	8(4.1%)	1(0.5%)	9(4.6%)	P=0.619
41-50yrs	10(5.2%)	0	10(5.2%)	
>51yrs	7(3.6%)	0	7(3.6%)	
Total	182(94.3%)	11(5.7%)	193(100%)	

Table-2: Comparison between type of HLA matching and BKV positivity.

HLA Matching	BKV Negative	BKV Positive	Total	
Allotransplant	153 (79.3%)	11 (5.7%)	164(85%)	
Auto transplant	19(9.8%)	0	19(9.8%)	P = 0.357
Haplotransplant	10(5.2%)	0	10(5.2%)	
Total	182(94.3%)	11(5.7%)	193(100%)	

Table-3: Detailed medical record of BKV positive patients.

BKV Positive Patients	Age	Gender	Primary Disease	Development of haematuria days after transplant	CMV Reactivation	GVHD	Conditioning Regimen	Post-transplant immunosuppression	Treatment given	Outcome
Patient 1	8yrs	Male	B-Thalassemia Major	Day 10	Yes	Yes	Fludarabine, Busalphan, Cyclophosphamide, Anti-thymocyte globulins	Cyclosporine, Methotrexate	Supportive	Alive
Patient 2	8yrs	Male	B-Thalassemia Major	Day 1 and worsened at day 13. Haematuria did not settle till his last day.	Yes	Yes (Gut)	Fludarabine, Busalphan, Cyclophosphamide, Anti-thymocyte globulins	Cyclosporine, Methotrexate	Oestrogen, oxybutynin, platelet transfusion	Dead
Patient 3	11yrs	Female	B-Thalassemia Major	Details not available	Yes	Yes	Fludarabine, Busalphan, Cyclophosphamide	Cyclosporine, Methotrexate	-	Dead
Patient 4	3yrs	Male	B-Thalassemia Major	Day 61	Yes	Yes	Fludarabine, Cyclophosphamide, Anti-thymocyte globulins	Cyclosporine, Methotrexate	Cidofovir 3 doses	Not known
Patient 5	12yrs	Female	B-Thalassemia Major	Details not available	Yes	Yes	Fludarabine, Busalphan, Cyclophosphamide	Cyclosporine, Methotrexate	-	Not known
Patient 6	9yrs	Male	B-Thalassemia Major	Day 27	Yes	Yes (Gut)	Fludarabine, Busalphan, Cyclophosphamide	Cyclosporine, Methotrexate	-	Not known
Patient 8	17yrs	Male	Chronic Myeloid Leukaemia	Day 74	Yes	Yes (Skin)	Fludarabine, Cyclophosphamide, Anti-thymocyte globulins	Cyclosporine, Methotrexate, Mycophenolate	Conservative mycophenolate omitted	Alive
Patient 9	8yrs	Female	B-Thalassemia Major	Day 45	Yes	Yes (Skin)	Fludarabine, Busalphan, Cyclophosphamide	Cyclosporine later stopped and tacrolimus started	Conservative leflunomide, IVIG and oestrogen	Dead
Patient 10	18yrs	Male	Acute Lymphoid Leukaemia	Day 50	Yes	Yes (Lung)	Busalphan, Cyclophosphamide, Anti-thymocyteglobulins	Cyclosporine, Methotrexate, Mycophenolate	Conservative, oral oestrogen, leflunomide, Clot evacuation under GA, cidofovir 2 doses	Alive
Patient 11	33yrs	Male	Acute Myeloid Leukaemia	Day 30	Yes	Yes	Busalphan, Cyclophosphamide, Anti-thymocyte globulins	Cyclosporine, Methotrexate, Mycophenolate	Conservative	Dead

Data analysis showed that, although the p-value was not significant, most of the patients who developed HC associated with BKV were in the youngest age group i.e. 3 months to 10 years and this frequency decreased gradually with increasing age of the patients, as shown in Table-1.

All 11 (100%) cases with BKV associated HC were seen in allotransplant recipients, and no case was reported in autotransplant and haplotransplant patients (Table-2).

Medical records of BKV positive patients were studied in detail as shown in Table-3. Out of the 11 positive cases, 7 patients had B-Thalassemia Major as primary disease, 01 case was of aplastic anaemia, 01 of Chronic Myeloid Leukaemia and 2 cases of acute leukaemia. All these patients developed CMV reactivation with some degree of graft versus host disease. The patients were followed over a period of two years. Post-transplant patients are discharged once they are stable. After that they are followed twice weekly for first two weeks, followed by once weekly visit for next two weeks. If they remain asymptomatic for one month, they are followed twice a month for six months and then once a month for the time they remain on immunosuppression. The patients can report anytime if they develop any symptoms. Among them, 04 patients survived, while 04 patients expired and the outcome of 3 patients was not known due to loss of follow-up.

Discussion

HC is a serious concern in allogenic HSCT patients with haematological disorders. Grade 1 and 2 HC corresponds to the presence of microscopic and macroscopic haematuria respectively, while grade 3 and 4 are associated with clots and severe bladder haemorrhage with renal impairment. According to the new perspective, BKV acts as a trigger for immune response and this leads to preventive testing in post-transplant cases.[8] In this study a detailed analysis of BKV HC cases in our setup has been provided. Majority of the cases in this study were males <40 years of age. Also, all of them developed CMV viraemia and GVHD. Primary disease in majority of cases (7 out of 11 positive cases) was B-thalassemia major as it is a prevalent genetic haematological disorder in our country.[9] Development of HC in B-thalassemia major patients was more as they receive intense conditioning regimen. A Korean study on allogenic SCT recipients due to multiple haematological disorders showed that out of 69 patients, 30 (43.5%) developed HC and 18 (60%) cases were BKV positive by PCR. The overall percentage of BKV positive HC cases in this study was high as compared with our study.[1]

Rorije et al from Netherland evaluated 491 patients undergoing transplant between January 2010 and December 2011 and BKV disease was found in 78 (15.9%) cases. All cases developed CMV reactivation and GVHD which was also observed in our study.[10] Lauran and colleagues evaluated HC in a large cohort (n=1,321) receiving alloHSCT (in Division of Haematology-Oncology and Transplantation, Department of Medicine, University of Minnesota, Minneapolis, USA). BK viruria was detected in 90% of HC patients which is similar to our study in which all cases of HC were PCR positive for BKV on urine sample. In this study, BKV HC was more commonly seen in male patients which is again similar to that in our study where 8 out of 11 positive patients were male.[11] Studies have suggested that there is a correlation between GVHD and HC or it is the immunosuppressive therapies used to treat GVHD that increase the chance of opportunistic infections that subsequently result in HC. Maha et al reported that younger age was independently associated with HC. Also, in our study, all BKV positive patients were <40 years of age.[12]

Conclusion

A high frequency of cases of BKV associated haemorrhagic cystitis is observed in young patients, i.e. three months to 10 years of age. Males were affected more than the females. All the patients with haemorrhagic cystitis were positive for BKV, had CMV reactivation and GVHD. Primary disease in most of the cases was Beta-Thalassemia Major which is highly prevalent in Pakistan.

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Conflict of Interests: None.

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References

1. Park YH, Lim JH, Yi HG, Lee MH, Kim CS. BK Virus-Haemorrhagic Cystitis Following Allogeneic Stem Cell Transplantation: Clinical Characteristics and Utility of Leflunomide Treatment. Turk J Haematol. 2016; 33:223-30.
2. Philippe M, Ranchon F, Gilis L, Schwiertz V, Vantard N, Ader F, et al. Cidofovir in the Treatment of BK Virus-Associated Haemorrhagic Cystitis after Allogeneic Haematopoietic Stem Cell Transplantation. Biol Blood Marrow Transplant. 2016; 22:723-30.
3. Cesaro S, Dalianis T, Hanssen Rinaldo C, Koskenvuo M, Pegoraro A, Einsele H et al. ECIL guidelines for the prevention, diagnosis and treatment of BK polyomavirus-associated haemorrhagic cystitis in haematopoietic stem cell transplant recipients.J Antimicrob Chemother. 2018; 73:12-21.
4. Jacobi J, Prignitz A, Büttner M, Korn K, Weidemann A, Hilgers KF, et al. BK viremia and polyomavirus nephropathy in 352 kidney transplants; risk factors and potential role of mTOR inhibition. BMC Nephrol. 2013; 14:207.
5. Gupta N, Lawrence RM, Nguyen C, Modica RF. Review article: BK virus in systemic lupus erythematosus. Pediatr Rheumatol Online

J. 2015; 13:34.
6. Dropulic LK, Jones RJ. Polyomavirus BK infection in blood and marrow transplant recipients. Bone Marrow Transplant. 2008; 41:11-8.
7. Lee SS, Ahn JS, Jung SH, Ahn SY, Kim JY, Jang HC, et al. Treatment of BK virus-associated haemorrhagic cystitis with low-dose intravenous cidofovir in patients undergoing allogeneic haematopoietic cell transplantation. Korean J Intern Med. 2015; 30:212-18.
8. Mert D, Batgi H, Merdin A, Çeken S, Dal MS, Tekgündüz E, et al. BK virus-associated haemorrhagıc cystitis in patients wıth allogenic haematopoıetıc cell transplantation:report of three cases. Haematol Rep. 2017; 9:7205.
9. Shahzad A, Rafiq N, Ullah I, Asad MJ, Ahmad MS, Waheed U, et al. Knowledge, attitude and practices (KAP) of the families of b-thalassaemia children in thalassaemia centres of Rawalpindi and Islamabad, Pakistan. J Pak Med Assoc. 2017; 67:1434-37.
10. Rorije NM, Shea MM, Satyanarayana G, Hammond SP, Ho VT, Baden LR, et al. BK virus disease after allogeneic stem cell transplantation: a cohort analysis. Biol Blood Marrow Transplant. 2014; 20:564-70.
11. Lunde LE, Dasaraju S, Cao Q, Cohn CS, Reding M, Bejanyan N, et al. Haemorrhagic cystitis after allogeneic haematopoietic cell transplantation: risk factors, graft source, and survival. Bone Marrow Transplant. 2015; 50:1432-7.
12. El-Zimaity M, Saliba R, Chan K, Shahjahan M, Carrasco A, Khorshid O, et al. Haemorrhagic cystitis after allogeneic haematopoietic stem cell transplantation: donor type matters. Blood. 2004; 103:4674-80.