

BK virus-associated hemorrhagic cystitis in patients with allogeneic hematopoietic cell transplantation: report of three cases

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Abstract

BK virus is a human polyoma virus. It is acquired in early childhood and remains life-long latent in the genitourinary system. BK virus replication is more common in receiving immunosuppressive therapy receiving patients and transplant patients. BK virus could cause hemorrhagic cystitis in patients with allogeneic stem cell transplantation. Hemorrhagic cystitis is a serious complication of hematopoietic stem cell transplantation. Hemorrhagic cystitis could cause morbidity and long stay in the hospital. Diagnosis is more frequently determined by the presence of BK virus DNA detected with quantitative or real-time PCR testing in serum or plasma and less often in urine. The reduction of immunosuppression is effective in the treatment of BK virus infection. There are also several agents with anti-BK virus activity. Cidofovir is an active agent against a variety of DNA viruses including poliovirus and herpesviruses and it is a cytosine nucleotide analogue. Intravenous immunoglobulin IgG (IVIG) also includes antibodies against BK and JC (John Cunningham) viruses. Hereby, we report three cases of hemorrhagic cystitis. Hemorrhagic cystitis developed in all these three cases of allogeneic stem cell transplantation due to acute myeloid leukemia (AML). BK virus was detected as the cause of hemorrhagic cystitis in these patients. Irrigation of the bladder was performed. Then levofloxacin 1×750 mg intravenous and IVIG 0.5 gr/kg were started. But the hematuria did not decreased. In the first case, treatment with leflunomide was started, but patient died due to refractory AML and severe graft-versus-host disease after 4th day of leflunomide and levofloxacin treatments. Cidofovir treatment

and the reduction of immunosuppressive treatment decreased the BK virus load and resulted symptomatic improvement in the second case. Initiation of cidofovir was planned in the third case. Administration of cidofovir together with the reduction of immunosuppression in the treatment of hemorrhagic cystitis associated with BK virus in allogeneic stem cell transplant recipients could be a good option.

Introduction

BK virus is a human polyoma virus that is acquired in childhood. It remains latent in the genitourinary system for whole life.¹ It could cause more frequent and higher grade viraemia in immunosuppressed patients.² The use of specific immunosuppressive agents and the intensity of immunosuppression could effect the risk of BK virus replication and the the progression of clinical disease in transplant recipients.³ BK virus could cause hemorrhagic cystitis in allogeneic stem cell transplant (ASCT) recipients.⁴ Hemorrhagic cystitis could cause morbidity and long term hospital stay.⁵ Acute hemorrhagic cystitis following engraftment in hematopoietic stem cell transplant recipients could be associated with BK virus.⁶ Clinical diagnosis could be put by detecting BK virus DNA by quantitative or real-time (polymerase chain reaction) PCR in plasma or serum and less frequently in urine.⁷ In this article, we present three allogeneic stem cell transplanted patients with hemorrhagic cystitis associated BK virus.

Case Report #1

A 43-year-old female patient with the diagnosis of acute myeloid leukemia-M6 (AML-M6) was admitted to the hematology inpatient 3 + 7 (standard dose cytosine, arabinoside and idarubicin) chemotherapy was given to the patient. She went into complete remission and after that she received 1 course of HIDAC (high dose cytarabine) chemotherapy. ASCT was done after 3 months. Graft-versus-host disease (GVHD) was developed in the patient. Methylprednisolone, cyclosporine and mycophenolate mofetil therapy were started. Macroscopic hematuria was developed in the patient after three months of the stem cell transplantation. Hemoglobin (Hb): 11.8 gr/dL, hematocrit (Htc): 33.8%, white blood cell (WBC): 1930/μL (neutrophil: 450/μL), platelet: 52,000/μL, creatinine: 1.21 mg/dL, blood urea nitrogen (BUN): 18 mg/dL, uric acid: 4.4 mg/dL and C-reactive protein

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(CRP): 4.7 mg/dL (0-5) in laboratory tests. Because of the febrile neutropenic attack, piperacillin-tazobactam 3×4.5 mg intravenous (IV) was started empirically. Blood and urine cultures were taken in patient with high fever. The urine culture, gram staining, tuberculosis culture, ARB (acid resistant bacteria) staining, BK virus PCR and adenovirus PCR tests were taken for differential diagnosis. BK virus PCR: 20.763.373 copies/mL was detected. Other tests were negative. The bladder irrigation and reduction of immunosuppressive treatment decreased hematuria. BK virus PCR: 3.760.719.465 copies/mL were detected in the control. Creatinine level increased to 3.34 mg/dL and nephritis was considered as secondary to BK virus. However, biopsy could not be performed due to low platelet counts. Hemodialysis was initiated to the patient. Leflunomide 3×100 mg tb, levofloxacin 1×500 mg IV and 0.5 g/kg intravenous immunoglobulin G (IVIG) were started to patient. The patient was admitted to the intensive care unit due to the clinical regression. The patient died due to refractory AML and severe GVHD after 4th day of leflunomide and levofloxacin treatments.

Case Report #2

A 64-year-old male patient with AML secondary to myelofibrosis was admitted to the Bone Marrow Transplantation Service (BMTS) for ASCT. The hematuria was developed in the patient at 33th day after

transplantation. Hb: 7.6 gr/dL, Htc: 22.7%, WBC: 590/ μ L (neutrophil: 54/ μ L), platelets: 28,000/ μ L, creatinine: 1.13 mg/dL, BUN: 30 mg/dL, uric acid: 5.7 mg/dL, CRP: 27.65 mg/dL in laboratory tests. A 10 mm diameter cortical cyst was detected in the right kidney in the abdomen USG. Bladder irrigation was started with 12 liters isotonic per day. The hematuria decreased. BK virus PCR: 163,000,000 copies/mL were detected. Other tests were negative. Because of hemorrhagic cystitis, IVIG 0.5 g/kg and levofloxacin 1 \times 750 mg IV were started to the patient. Clots were detected in the bladder in control abdomen USG. The patient underwent cystoscopy and the clots were evacuated. BK virus PCR: 580.800.000 copies/ml were detected. The patient's immunosuppressive treatment was reduced. Cidofovir treatment was started at 5 mg/kg once in a week for two weeks, continued after then every two weeks. After 1 month, BK virus PCR: 46.120 copies/mL were detected and treatment continued. The hematuria decreased. One month later BK virus PCR: 17.080 copies/mL was detected again. The patient's treatment continued. Symptoms of the patient improved. The treatment of the patient was completed after 3 months. The BK virus PCR was detected as negative for control purposes.

Case Report #3

A 20-year-old AML-M6 male patient with remission was admitted to the BMTS for ASCT. The patient was gone into ASCT. Acute GVHD developed after the transplant. Methylprednisolone, cyclosporine and mycophenolate mofetil treatment were started. Hematuria developed in the patient after the 30th day of transplantation. Hb: 5.7 gr/dL, Htc: 16%, WBC: 5.860/ μ L (Neutrophil: 5.370 / μ L), platelets: 55.000 μ L, creatinine: 1.28 mg/dL, BUN: 52 mg/dL, uric acid: 6.8 mg/dL in laboratory tests. 28 leukocytes and 328 erythrocytes were detected in the urine microscopy. The bladder irrigation was started with 12 liters of isotonic per day. Hematuria complaints of the patient increased. BK virus PCR: 905.080.070 copies/mL were detected. IVIG 0.5g/kg IV and levofloxacin 1 \times 750 mg IV were started. But hematuria did not decrease. Cidofovir therapy is scheduled to be given at 5 mg/kg once a week for two weeks followed by once in two week period. However, the patient's general condition went worse and the patient was admitted to the intensive care unit. The patient died because of refractory AML and severe GVHD before cidofovir treatment.

Discussion and Conclusions

BK virus could cause hemorrhagic cystitis in allogeneic stem cell transplantation patients.⁴ Hemorrhagic cystitis is a serious complication of hematopoietic stem cell transplantation. It could cause to morbidity and long term hospital stay.⁵ In a study conducted by Arthur *et al.* BK virus was detected in 53 hematopoietic stem cell transplant recipients.⁶ ASCT were performed in three of our cases. Hemorrhagic cystitis developed after 3th month of transplantation in the first case and hemorrhagic cystitis developed after approximately 1 months after transplantation in the other 2 cases. BK virus was detected as the cause of hemorrhagic cystitis. The use of quantitative or real-time PCR to detect BK virus DNA has been shown to be useful in plasma or serum, less frequently in urine in following renal transplant recipients.⁷ In all of the three cases, BK virus was detected in urine by real-time PCR test.

The reduction of immunosuppression was known to be effective in the treatment of BK virus infection. The reduction of immunosuppression was found to be successful in elimination of viremia in a single-center study with 24 patients.⁸ Several agents with anti-BK virus activity were demonstrated.⁹ The cidofovir is cytosine nucleotide analogue and it is an active agent against various DNA viruses including poliomyelitis viruses.¹⁰ In a retrospective nonrandomized study, 8 of 21 patients were treated with weekly low-dose cidofovir administration and immunosuppression reduction, only 13 patients were treated with reduced immunosuppressive therapy.¹¹ In another study, clinical response was obtained in all adult patients treated with cidofovir (16/19, 84%); but only 9 of 19 patients (47%) were detected reduction greater than 1 log in the BK virus load in urine.¹² In a study conducted by Cesaro *et al.*,¹⁴ (81%) of 27 patients had a complete clearance of BK virus associated hemorrhagic cystitis after the introduction of cidofovir on the average 37 days.¹³ Cidofovir treatment and the reduction of immunosuppressive treatment was started to the patient. 1 log decreased in BK virus load after 1st month of cidofovir treatment. Hematuria was regressed in case 2.

Leflunomide is a prodrug. Anti-metabolite of leflunomide is A77 1726. Both have immunosuppressive and antiviral activities.¹⁵ The mechanism of action against BK virus is unknown.¹⁶ In the case series, leflunomide improved in 23 of 26 patients with BK virus nephropathy.¹⁷ Leflunomide treatment was started in one of

our cases; but the patient died because of refractory AML and severe GVHD after 4 days. IVIG contain antibodies against to BK and JC (John Cunningham) viruses. Three of the our patients received IVIG. Quinolone antibiotics have anti-BK virus activities.¹⁸ Levofloxacin was given as a treatment or as a prophylactic agent in the treatment of active BK viremia in two randomized trials.¹⁹ BK virus was detected as the cause of hemorrhagic cystitis in our cases. The cidofovir treatment and the reduction of immunosuppressive treatment caused to improve symptoms and findings. They caused to decrease in the BK virus load.

Intravenous immunoglobulin G contain antibodies against JC and BK virus. These viruses are ubiquitous in the general population. But, these antibodies not be neutralizing.^{20,21} Other studies indicate that the anti-BK antibodies are not protective and these antibodies indicate an augmented humoral response to an inadequate cellular immune response.²² IVIG 0.5 g/kg IV was started in case 2 and case 3. But hematuria did not decrease in these cases.

In this article, it is aimed to emphasize that cidofovir treatment with reducing immunosuppressive treatment is a good alternative in the treatment of hemorrhagic cystitis associated with BK virus in the allogeneic stem cell transplant recipients.

References

1. Hirsch HH. BK virus: opportunity makes a pathogen. *Clin Infect Dis* 2005;41:354-60.
2. Peinemann F, de Villiers EM, Dörries K, et al. Clinical course and treatment of haemorrhagic cystitis associated with BK type of human polyomavirus in nine paediatric recipients of allogeneic bone marrow transplants. *Eur J Pediatr* 2000;159:182-8.
3. Gralla J, Huskey J, Wiseman A. Trends in immune function assay (ImmuKnow, Cylex) results in the first year post-transplant and relationship to BK virus infection. *Nephrol Dial Transplant* 2012;27:2565-70.
4. Hirsch HH. Polyoma and papilloma virus infections after hematopoietic stem cell or solid organ transplantation In: Bowden P, Ljungman P, Snyderman DR (Eds). *Transplant infections*. Philadelphia: Lippincott Williams & Wilkins; 2010. p 465.
5. Silva Lde P, Patah PA, Saliba RM, et al. Hemorrhagic cystitis after allogeneic hematopoietic stem cell transplants is the complex result of BK virus infec-

- tion, preparative regimen intensity and donor type. *Haematologica* 2010;95:1183-90.
6. Arthur RR, Shah KV, Baust SJ, et al. Association of BK viremia with hemorrhagic cystitis in recipients of bone marrow transplants. *N Engl J Med* 1986;315:230-34.
 7. Randhawa P, Vats A, Shapiro R. Monitoring for polyomavirus BK and JC in urine: comparison of quantitative polymerase chain reaction with urine cytology. *Transplantation* 2005;79:984-6.
 8. Saad ER, Bresnahan BA, Cohen EP, et al. Successful treatment of BK viremia using reduction in immunosuppression without antiviral therapy. *Transplantation* 2008;85:850-4.
 9. Josephson MA, Williams JW, Chandraker A, Randhawa PS. Polyomavirus-associated nephropathy: update on antiviral strategies. *Transpl Infect Dis* 2006;8:95-101.
 10. Vandercam B, Moreau M, Goffin E, et al. Cidofovir-induced end-stage renal failure. *Clin Infect Dis* 1999;29:948-9.
 11. Kuypers DR, Vandooren AK, Lerut E, et al. Adjuvant low-dose cidofovir therapy for BK polyomavirus interstitial nephritis in renal transplant recipients. *Am J Transplant* 2005;5:1997-2004.
 12. Savona MR, Newton D, Frame D, et al. Low-dose cidofovir treatment of BK virus associated hemorrhagic cystitis in recipients of hematopoietic stem cell transplant. *Bone Marrow Transplant* 2007;39:783-7.
 13. Cesaro S, Hirsch HH, Faraci M, et al. Cidofovir for BK virus associated hemorrhagic cystitis: a retrospective study. *Clin Infect Dis* 2009;49:233-40.
 14. Cesaro S, Pillon M, Tridello G, Aljurf M, et al. Relationship between clinical and BK virological response in patients with late hemorrhagic cystitis treated with cidofovir: a retrospective study from the European Group for Blood and Marrow Transplantation. *Bone Marrow Transplant* 2013;48:809-13.
 15. Chong AS, Zeng H, Knight DA, et al. Concurrent antiviral and immunosuppressive activities of leflunomide in vivo. *Am J Transplant* 2006;6:69-75.
 16. Farasati NA, Shapiro R, Vats A, Randhawa P. Effect of leflunomide and cidofovir on replication of BK virus in an in vitro culture system. *Transplantation* 2005;79:116-8.
 17. Josephson MA, Gillen D, Javaid B, et al. Treatment of renal allograft polyoma BK virus infection with leflunomide. *Transplantation* 2006;81:704-10.
 18. Gabardi S, Waikar SS, Martin S, et al. Evaluation of fluoroquinolones for the prevention of BK viremia after renal transplantation. *Clin J Am Soc Nephrol* 2010;5:1298-304.
 19. Knoll GA, Humar A, Fergusson D, et al. Levofloxacin for BK virus prophylaxis following kidney transplantation: a randomized clinical trial. *JAMA* 2014;312:2106-14.
 20. Bohl DL, Brennan DC, Ryschkewitsch C, et al. BK virus antibody titers and intensity of infections after renal transplantation. *J Clin Virol* 2008;43:184-9.
 21. Randhawa P, Bohl D, Brennan D, et al. Longitudinal analysis of levels immunoglobulins against BK virus capsid proteins in kidney transplant recipients. *Clin Vaccine Immunol* 2008;15:1564-71.
 22. Bohl DL, Storch GA, Ryschkewitsch C, et al. Donor origin of BK virus in renal transplantation and role of HLA C7 in susceptibility to sustained BK viremia. *Am J Transplant* 2005;5:2213-21.