

After allogenic bone marrow transplantation agent of hemorrhagic cystitis: BK virus^{*}

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ABSTRACT

Hemorrhagic cystitis is a common and in its severe form potentially life threatening complication of hematopoietic stem cell transplantation. Hemorrhagic cystitis is defined as a diffuse inflammatory condition of the urinary bladder due to an infectious or noninfectious etiology resulting in bleeding from the bladder mucosa. Hemorrhagic cystitis is characterized by lower urinary tract symptoms including dysuria, hematuria and hemorrhage. The most common cause is a bacterial infection that usually responds promptly to treatment. But chronic and recurrent hemorrhagic cystitis often arises from anticancer chemotherapy or radiotherapy for the treatment of pelvic malignancies. Infectious etiologies are less common causes of chronic hemorrhagic cystitis except in immunocompromised hosts like bone marrow transplant recipients. Hemorrhagic cystitis is a significant complication of bone marrow transplantation which influences economic and survival outcome. Hemorrhagic cystitis can be divided into two classes according to onset time; early and late onset time. Early-onset hemorrhagic cystitis is commonly associated used with chemo-radiotherapy protocols in some of the preparatory regimens. More than one factor is accused in the etiology of late onset hemorrhagic cystitis. Here, we present a patient whose hematuria started after 54 days from allogeneic stem cell transplantation.

Keywords: Allogenic Bone Marrow Transplantation;

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Hemorrhagic Cystitis; BK Virus

1. INTRODUCTION

Hemorrhagic cystitis is described as a diffuse inflammatory condition of the urinary bladder due to an infectious or noninfectious etiology resulting in bleeding from the bladder mucosa. Hemorrhagic cystitis is differentiated into two types according to onset time; early and late onset hemorrhagic cystitis [1].

Early-onset hemorrhagic cystitis commonly associates with chemo-radiotherapy used in the preparation regimens. Especially, hemorrhagic cystitis emerges as a result of high dose cyclophosphamide and ifosfamide treatments. The dose of cyclophosphamide is associated with the risk of hemorrhagic cystitis. If prophylaxis is not used for hemorrhagic cystitis in cases with hematopoietic stem cell transplantation, the risk of hemorrhagic cystitis has increased. Hematuria is the most frequently occurred after two weeks of preparation regimen. On the other hand, hemorrhagic cystitis can start immediately or three months later after application of cyclophosphamide. Risk is increased in patients who had pelvic irradiation and busulfan treatment. Allogeneic transplant patients and elderly patients have an additional risk in terms of hemorrhagic cystitis [2].

Multiple factors are accused in the etiology of late-onset hemorrhagic cystitis. Generally, this type of hemorrhagic cystitis occurs after weeks or months from transplantation. A history of hemorrhagic cystitis attack is the most important risk factor for another attack. Viruses and graft versus host disease (GVHD) are also accused in the etiology of hemorrhagic cystitis. The BK polyoma virus, adenovirus, cytomegalovirus (CMV), JC virus, Epstein Barr virus (EBV) and herpes virus have been implicated in the etiology of hemorrhagic cystitis. Suitable hosts for

these viruses are immunosuppressed patients. GVHD and hemorrhagic cystitis are another issue discussed in the literature [1].

The BK virus is a member of the polyoma virus family. BK virus is highly prevalent in the population and is thought to remain dormant and asymptomatic in the kidney and other organs after the initial infection. When the immune system is compromised, as in persons undergoing chemotherapy after bone marrow, stem cell and solid organ transplantation, the virus gets reactivated leading to cystitis. BK virus has been reported to cause hemorrhagic cystitis in 5.7% to 7.7% of bone marrow transplant recipients. Early diagnosis and treatment of viral cystitis may prevent significant morbidity of hemorrhagic cystitis. The diagnosis is based on molecular techniques and real-time polymerase chain reaction (PCR), which allows quantification of viral load is often the method of choice [3]. Although no drug is yet licensed for use in BK virus infection, cidofovir is becoming the drug of choice in viral hemorrhagic cystitis in immunosuppressed patients because it is active against the most common viral pathogens. Leflunomide has been shown to significantly reduce BK viral load in blood and urine in renal transplant patients with biopsy proven BK nephropathy [4]. Ciprofloxacin may have a prophylactic role in preventing BK viral cystitis in bone marrow transplant patients [5]. Hyperbaric oxygen in the treatment of refractory hemorrhagic cystitis can be used successfully in patients [6].

Here, we present a case of hemorrhagic cystitis due to BK virus infection in an acute myeloid leukemia patient was treated with allogeneic stem cell transplantation.

2. CASE PRESENTATION

A 40 years old female patient was diagnosed acute myeloid leukemia and idarubicine 1×12 mg/m²/day (3 days), cytarabine 1×100 mg/m²/day (7 days) therapies as induction and 3 cycles of high-dose cytarabine (2×3 g/m²/day) therapy for consolidation were given successfully. After these treatments, the patient was applied seamlessly allogeneic stem cell transplantation from HLA matched siblings with BU-CY (busulfan-cyclophosphamide) protocol (busulfan 4×0.8 mg/kg/day (4 days), cyclophosphamide 60 mg/kg/day (2 days), mesna 90 mg/kg/day (2 days) in bone marrow transplantation unit. Although the patient did not have hematuria before he experienced a gross hematuria episode in fifty second day of transplantation. Physical examination revealed marked suprapubic tenderness. A complete blood count revealed hemoglobin 8.8 g/dL, leukocyte 2.100/microL, neutrophil 1.500/microL, lymphocyte 500/microL, and platelets 22.000/microL. Peripheral blood smear was compatible with blood count. International normalized ratio (INR), Activated Partial Thromboplastin Time (APTT),

and serum creatinine levels were normal. C-reactive protein concentration was moderately elevated as 3.2 mg/dL. The red color of urine was seen only in the sediment (and the supernatant was not red). Bacterial or fungi infection were not seen in the cytobacteriological examination of urine samples. Nephrolithiasis, or other bladder pathologies causing of hematuria were not seen in radiographic examinations including ultrasonography, non-contrast computed tomography of abdomen and pelvis. Medication usage history in terms of hemorrhagic cystitis was negative. Hemocultures and urine cultures were negative. The patient was not using drugs like anticoagulants at this time and patient was using treatments like cyclosporine (2×150 mg/day/i.v), methyl prednisolone (1×120 mg/day/i.v) and intravenous immune globulin (5 gr/day/i.v once a week to 100th day) for GVHD and infection prevention. After excluding other causes of hematuria, urine analysis with polymerase PCR analysis revealed positive BK virus. Real-time PCR for adenoviruses was negative. We could not analyze the other viruses. Platelet suspension was given and then platelet counts was detected 72.000/microL, but gross hematuria persisted. Erythrocyte suspension was transfused intermittently as supporting treatment. We stopped methyl prednisolone and reduced dose of cyclosporine (2×50 mg/day/i.v). We gave ciprofloxacin (2×400 mg/day/i.v for 14 days) treatments. Continuous bladder irrigation was performed with three way foley urethral catheter. Cystoscopy was applied and hemorrhagic foci was cauterized by consulting with the department of urology and nephrology clinics (**Figure 1**). After one month of mentioned treatments above blood in the urine decreased slowly. We applied control cystoscopy, revealing recovery of hemorrhagic foci (**Figure 2**), and blood in the urine stopped without need of any other treatments. Control BK virus PCR result was negative.

3. DISCUSSION

Hemorrhagic cystitis after allogeneic stem cell trans-



Figure 1. Cystoscopic view of the bladder showing the widespread bleeding areas on the bladder mucosa.



Figure 2. Cystoscopic image after one month of treatment minimal local hemorrhagic area on the bladder mucosa.

plantation is one of the most common causes of morbidity and mortality in patient with stem cell transplantation. Hemorrhagic cystitis can be emerged in the early or late phase of stem cell transplantation [1]. In our patient, hemorrhagic cystitis was seen in fifty second day after allogeneic stem cell transplantation. The patient was evaluated with X-ray, ultrasonography and non-spiral CT of urinary tract, urine analysis, urine culture for diagnosis of hemorrhagic cystitis. Thus, among the main causes of hematuria like stone, simple infections were eliminated and the patient was diagnosed late onset hemorrhagic cystitis.

A grading system for severity of hemorrhagic cystitis has been proposed by Droller *et al.* for hemorrhagic cystitis [7]. We accepted our patient. Stage III (macroscopic hematuria with small clots) hemorrhagic cystitis and we searched for causes of late onset hemorrhagic cystitis.

A history of hemorrhagic cystitis episode is a main risk factor for late onset hemorrhagic cystitis. In addition, viruses (BK virus, adenovirus, and CMV) and GVHD are accused for hemorrhagic cystitis. Our patient did not has a history of hemorrhagic cystitis. There was no signs like skin rash, diarrhea, and abnormal liver function tests which could support a diagnosis of acute GVHD. We evaluated the urine analysis with PCR method for CMV, adenovirus and BK virus. PCR result for BK virus was positive. The cornerstone of therapy for hemorrhagic cystitis due to BK virus is reduction of immunosuppression. Studies showed that overall immunosuppressive load is more important than a single immunosuppressive agent use in terms of BK virus infections [8]. In our patient we thought the cause of BK virus infection as immunosuppressive load and dose of cyclosporine treatment was reduced to 2×50 mg/day/i.v.

In the literature, a large bore three-way foley urethral catheter insertion to decompress the bladder and saline solution irrigation of bladder is recommended as a first step treatment. This maneuver may slow or stop the

bleeding. In some instances cystoscopic clot evacuation may be necessary [1]. Continuous irrigation was applied for 30 days by consulting with the department of urology and nephrology clinics. Cystoscopy was performed to treat hematuria and hemorrhage foci were cauterized by urology clinic.

Other therapeutic options include cidofovir, leflunomide, intravenous immunoglobulin, and fluoroquinolones for BK virus infection. Cidofovir is a nucleotide analogue of cytosine that is active against various DNA viruses. Cidofovir may have activity against BK virus [9]. Leflunomide reduces BK viral load in blood and urine in renal transplant patients with BK nephropathy [4]. Limited data is available concerning the efficacy of intravenous immune globulin in patients with BK nephropathy [10]. The efficacy of ciprofloxacin, was best reported in a study of 68 hematopoietic stem cell transplantation patients. These informations support a role for ciprofloxacin in the prevention of BK viremia [5]. Hyperbaric oxygen in the treatment of refractory hemorrhagic cystitis is used successfully [6]. Our patient responded to reduce dose of immunosuppressive, ciprofloxacin treatment, intravenous immune globulin, continuous irrigation and cauterization.

4. CONCLUSION

BK virus infection must be kept when an allogeneic stem cell transplantation patient admitted with gross hematuria.

5. AUTHORS' CONTRIBUTIONS

This report reflects the opinion of the authors and does not represent the official position of any institution or sponsor. IB was responsible for reviewing previous research, journal hand searching, and drafting the report. FO and RA were responsible for provision of published trial bibliographies, and preparing photographs. MK, MAE and OU contributed to the final draft of the manuscript and analysis of relevant data. IK and EK was responsible for project coordination. All authors read and approved the final manuscript.

6. CONSENT

Written informed consent was obtained from the patient's next of kin for publication of this manuscript and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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ABBREVIATIONS

GVHD: Graft Versus Host Disease

CMV: Cytomegalovirus

EBV: Epstein Barr Virus

PCR: Polymerase Chain Reaction

BU-CY: Busulfan-Cyclophosphamide

INR: International Normalized Ratio

APTT: Activated Partial Thromboplastin Time