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Case Report Open Access

Recovery from Cidofovir-Resistent BK Virus-Associated Hemmorhagic Cystitis Post Cord Blood Transplant Following Rapid Taper of Immunosuppression

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Abstract

Hemorrhagic cystitis (HC) usually happens 2-4 weeks after Hematopoietic Stem Cell Transplantation (HSCT). BK virus associated HC is a severe complication after HSCT and usually sensitive to cidofovir treatment. Here we report a late onset BK virus-associated HC after a cord blood transplantation (HLA 5/6) followed by a failure treatment of cidofovir in an acute lymphoblastic leukemia patient. The patient was conditioned with an intensified conditioning regimen containing fludarabine, cytosine arabinoside, busulfan, cyclophosphamide and rabbit antithymocyte globulin (FABuCy+ATG). The late development of HC with the symptom of hematuria occurred 22 days after HSCT and was associated with BK virus. In two weeks, the hematuria progressed with the failure of hydration, alkalizing diuresis and reduction of immunosuppressant treatment. Surprisingly, treatment of cidofovir only transient lower BK virus copies and was proved to be a failure. Thereafter, early immunosuppressant withdrawal was applied followed by thymosin α1 injections to enhance immunity. Although the BKV was still high, HC recovered with mild and controllable GVHD. One year after HSCT, the patient remain well without HC as well as GVHD.

Keywords: Hemorrhagic cystitis; Cord blood transplantation; Cidofovir; Immunosuppressant; BK virus

Introduction

Cord blood transplant (CBT) provides an alternative for adults in hematologic malignancies patients, in which the stem cells resource from HLA-identical siblings is only about 30 percent [1,2]. Hemorrhagic cystitis (HC) is a complication with its incidence up to 40%, depending on virus infection, such as CMV, BKV, usage of ATG and cyclophosphamide, immunosuppression and the transplanted allograft [3]. Late onset HC is a common complication following CBT and is primarily associated with viral infection [4]. Generally the HC is scored according to several factors [5].

BKV is a polyoma virus from papovaviridae families. BK virus associated HC is a severe complication after HSCT and usually sensitive to cidofovir treatment. Its infection often occurs early in childhood, and the antibody seroprevalence in healthy population can be up to 80% [6]. Initial infection of BKV is asymptomatic. The virus can remain latent in the kidneys or urothelium after the initial infection. After CBT, the immunosuppression status can reactivate the BKV. This reactivation is thought to be associated with HC [7].

However, in those patients that do not develop HC, the BKV copies can be also very high [8], indicating other mechanism can be involved in late onset HC. Cidofovir, as well as levofloxacin, can be applied to the treatment of BK virus infection in patients undergoing allogeneic hematopoietic stem cell transplantation [9].

For the treatment of late onset HC, adequate hydration to induce brisk diuresis, continuous bladder irrigation, and treatment of urinary tract infections is important. After hemorrhagic cystitis develops, withdrawing/reducing immunosuppressant reagent can also be applied to treat the disease. Herein, we report a successful treatment case of cidofovir-resist BK virus-associated hemorrhagic cystitis by early immunosuppressant withdrawal after an HLA 5/6 CBT.

Case Report

A 19 yr-old Chinese Han girl with complaints of fever were admitted to Fujian Medical University Union Hospital. She had anemia for 3 weeks. Physical examination revealed tenderness of the chest and enlargement of lymph node. Blood count found WBC 73.2 × 10^9/L, Hb74 g/L, Plt34 × 10^9/L, Blast cell: 96%; Bone marrow aspiration showed acute lymphocytic leukemia (L2); Flowcytometry showed HLA-DR, CD13, CD15, CD19, CD20, CD22, CD34, CD38, CD123, cCD79a(+); Chromosome test showed 47, XX, + 10 [8]/46, XX [10-12]. She was diagnosed of ALL-B with HOX11 gene. Pethema ALL-96 regimen containing DNR, VCR, Pred, ASP and CTX were given to the patient to achieve complete remission. Due to the high risk of relapse and lack of donor, we performed CBT from a male donor (HLA 5/6) in a public cord blood bank.

In view of the patient's good perform status and high-risk to relapse, an intensified conditioning of fludarabine (30 mg/m^2 qd for four days), busulfan (9.6 mg/kg seperated into three days) cytosine arabinoside (2.0/m^2 qd for four days), cyclophosphamide (3.6 g/m^2 separated into 2 days) and rabbit antithymocyte globulin (ATG; 10 mg/kg) was selected to treat the patient. Four I.V. mesna doses (2.5 g/m^2 in total) were given at -1, 0, 3, and 6 hours after cyclophosphamide administration. An HLA mismatched (5/6) male cord blood cells (total nucleated cells: 3.71 × 10^7/kg, containing 3.4 × 10^5/kg of CD34-positive cells) were transplanted. After CBT, mycophenolate mofetil (MMF) and ciclosporin (CsA) were used to prevent GVHD. The time to neutrophil engraftment and plantlet engraftment were 16 days and

37 days separately. Full donor chimerism was found after engraftment by short tandem repeat (STR) detection.

The late development of HC with the symptom of hematuria occurred 22 days after transplantation and was associated with BK virus, but not EB-virus or cytomegalovirus (by polymease chain reaction detection). In two weeks, the hematuria progressed with the failure of hydration, alkalizing diuresis and reduce of immunosuppressant treatment (Figure 1). Surprisingly, treatment of cidofovir (5 mg/kg per week, with 2.0 g probenecid three hours before iv cidofovir and 1.0 probenecid 1 hour/8 hours after iv cidofovir) was found to be a failure (Figure 2). After the anti-virus treatment, the kidney function remained normal. The flowcytometry of peripheral blood showed very few T cells (CD3: 2.67%, CD4: 1.22%). Thereafter, early immunosuppressant withdrawal (CyA and MMF were suspended together, Figure 2) was applied followed by thymosin α1 injection (1.6 mg, BiW for two months) to enhance immunity. The flowcytometry showed enhanced T-cell immunity (CD3: 7.18%, CD4: 5.77%) after the rapid taper of immunosuppression. One month later, although the BKV was still high, HC recovered (Figures 1 and 2) with mild and controllable GVHD (I, skin). One year after HSCT, the patient remain well without HC as well as GVHD.

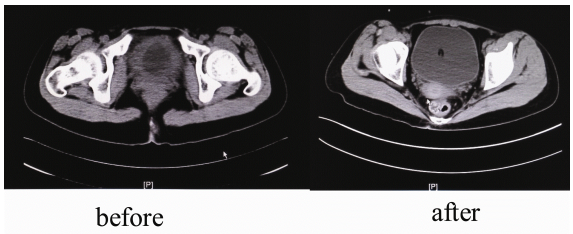

Figure 1: CT scan: A CT scan image was shown.(before: thickening of bladder wall due to HC; after: bladder wall return back to normal after withdrawal with still high BKV load).

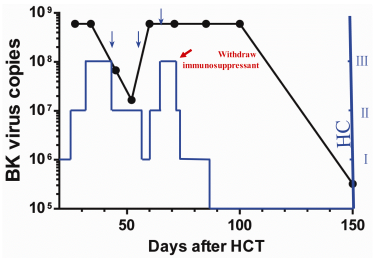

Figure 2: BK virus infection versus clinical HC: (left) Detection of the BK virus by PCR. Urine samples were collected and tested for BKV DNA by quantitative real time polymerase chain reaction analysis. Samples were test by Hightrust Diagnostic, Kindstar Global Co. BKV-DNA test kit was purchased from Beijing SinoMDgene Technology Co.,Ltd (YZB/6671-2012.3400075). BKV copies were shown. (right) Vertical axis (I to III): The clinical HC (the system score is indicated in ref.5, an article by Brugieres et al.). Blue arrows represent cidofovir (5 mg/kg) was given.

Discussion

HC is one of the complications CBT, which can happen at any stages [3]. Late onset HC happens 2 weeks after conditioning and is associated with virus infection [4]. Han [10] reported that cytomegalovirus is a potential risk factor of late-onset hemorrhagic cystitis following allogeneic hematopoietic stem cell transplantation. BKV and JCV is also reported to be associated with late onset HC [4]. It is reported that BK viruria is associated with an increased risk for HC in HSCT patients, but it is not diagnostic for HC. Also, a high BKV load in urine is indicative but not diagnostic for HC [11]. Here, we report an HC case associated with BKV after CBT.

Management of HC is supportive and still no specific treatment of late onset BKV-associated HC is available. Although some studies suggest antiviral drugs can be applied to the treatment of BKV-associated HC [9], randomized trials with different antiviral agents have not been conducted yet. There is a report showing low-dose cidofovir for BKV-associated HC may be effective [12,13]. In the present case, treatment of cidofovir only transient lower BK virus copies. The clinical response proved cidofovir treatment to be a failure, indicating that the virus could be cidofovir resisted. Current data indicate that the treatment alternatives for clinically failure of cidofovir is mostly unsatisfactory. Although some centers use other antiviral drugs (leflunomide, and/or ciprofloxacin) to treat patients, to date no definitive data have confirmed their effectiveness. However, reduction of immunosuppression does seem to have a relevant effect.

Thymosin is used in clinics to boost the immune response. It has been found to enhance cell-mediated immunity. It could be an important part of this successful HC treatment. HC patients are recommended hyperhydration and force diuresis. Urological intervention was also used to avoid renal failure due to massive clotting in this patient. The hematuria still progressed with the failure of hydration, alkalizing diuresis, cidofovir and the reduction of immunosuppressant treatment. Given the progression of HC, early immunosuppressant withdrawal was applied followed by thymosin α1 injections to enhance immunity. The present case showed little GVHD after the withdrawal. The patient recovered from HC with BK virus copies still high. This result suggested that, although BK viruria is associated with late onset HC in HSCT patients, BKV load might not be diagnostic for HC. Also, withdrawal of immunosuppression can be an alternative for HC.

It's worth noting that we withdrawal the immunosuppression early in the present CBT case. Those patients undergo haplo-identical HSCT or alternative HSCT should be paid more attention. Early withdrawal of immunosuppression drug might induce severe GVHD.

In conclusion, the ability of immune recovery is important to control HC. The "well performed" new immune system takes "good" control of viral-driven complications post transplant (relevant to PTLD, adenovirus, CMV, etc.). Here, we report a cidofovir-resist BK virus-associated hemorrhagic cystitis case after cord blood transplantation. This case is a successful treatment by early immunosuppressant withdrawal. The present case suggests that for those regular treatment failure patients of HC, especially for those BKV associated and antiviral treatment resist, early immunosuppressant withdrawal after HSCT could be a good way to cure HC.

Disclosure

The authors have no financial conflicts of interest.

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