CASE REPORT

A Rare Case of Hemorrhagic Cystitis in Allogeneic Hematopoietic Stem Cell Transplant Patient

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Abstract Post bone marrow transplant patients are susceptible to atypical infections, especially viral pathogens. The risk increases many folds in cases of allogeneic transplantation, which also receive GVHD prophylaxis. Viral pathogens like cytomegalovirus and herpes are the common ones encountered during follow-up period. However, in recent times there have been reports of a variety of disease manifestations of rare viruses like polyoma virus and adenovirus. These viral infections may play a crucial role in morbidity and mortality in immunocompromised patients. We hereby elaborate the follow-up course of a 36-year-old post allogeneic transplant patient of acute myeloid leukemia who developed adenovirus related haemorrhagic cystitis. Treatment with oral ribavirin lead to dramatic improvement in symptomatology within a week. This cases re-emphasizes the fact that after ruling out the commoner pathogens, it's of utmost importance to strongly consider the atypical pathogens in such cases.

Case-Report

A 36-year-old gentleman, known case of acute myeloid leukemia (FAB-M2) was admitted on Day +380 of allogeneic stem cell transplant with 7 days history of lower urinary tract symptoms (LUTS), dysuria, increased urine frequency, urgency of urine, and haematuria. In the background, patient received inj. busulphan (0.8 mg/kg every 6 h for 4 days) and inj. cyclophosphamide (60 mg/kg/day

for 2 days) as conditioning regimen. Peri-transplant period was unremarkable for any complication. No features of high dose cyclophosphamide induced cystitis or acute graft versus host disease (aGVHD) was noted. He received cyclosporine-A (5 mg/m²) and methotrexate 15 mg/m² on Day +1 and 10 mg/m² on Day +3, +6 and +11 as prophylaxis for GVHD (Fig. 1). Tapering of immunosuppression was started on Day +80 onwards and patient did not have any evidence of GVHD till Day +256. Following which he developed lichenoid changes in the oral mucosa, dryness of eyes and hypopigmented patches over the face and upper trunk involving <25 % of body surface (Fig. 2). Liver function tests showed total bilirubin levels-1.2 g/dL, SGOT, SGPT and SALP of 92, 139, 392 IU/mL, respectively. After clinical examination, laboratory evaluation and liver+skin biopsy he was diagnosed as moderate cGVHD (Table 1). As a result additional immunosuppressive medications in the form of mycophenolate (1000 mg BD) along with oral prednisolone was started. He also received topical cyclosporine eye drops (0.05 %) for conjunctival GVHD. Following immunosuppressive therapy symptoms related to GVHD started improving (Fig. 1; Table 1). However, he developed severe LUTS as mentioned above on Day +380. At this time he had macroscopic hematuria with frequent passage of clots. There was no pallor, suprapubic or renal angle tenderness. By this time, GVHD had improved significantly (with the cGVHD score as mentioned in Table 1: mucosa-0, skin-1, liver-0, and eye-1). Urine analysis showed all fields full of red blood cells. Total blood counts showed Hb-12.2 g/dL, TLC-7200/μL with normal differential counts and mild thrombocytopenia 98,000/μL. Renal parameters were within normal limits. A working diagnosis of grade III hemorrhagic cystitis (HC) was made as per criteria mentioned in Table 2 [1]. Urine culture was negative for

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Fig. 1 Follow up during post-transplant period showing the immunosuppressants used, grade of cGVHD at various interval of time and management of haemorrhagic cystitis

Fig. 2 **a** Brown to violaceous macules coalescing to form patches over face predominantly over the malar and forehead area. **b** Well to ill-defined erythematous, violaceous plaques over the glans penis. **c** Erythematous maculopapular rash predominantly over the thenar eminence

bacterial pathogens, therefore the possibility of single or combined opportunistic viral infections as a cause of HC was suspected in view of ongoing immunosuppression. Blood and urine investigations for quantitative PCR analysis was sent for cytomegalovirus (CMV), polyoma virus (BK/JC virus), adenovirus, herpes virus (HSV). NCCT KUB was done, which suggested diffusely inflamed and thickened bladder wall (Fig. 3). Cystoscopy was not done in view of risk of bladder perforation in the setting of active inflammation.

Table 1 cGVHD scoring based on organ involvement

Organ	Scoring at day +250	Scoring at day +375
Skin	2	1
Mouth	1	0
Eyes	2	1
GI tract	0	0
Genital examination	2	1
Liver	2	0
Grade of GVHD	Moderate	Mild

Table 2 Grading of haemorrhagic cystitis

Grading	Criteria
I	Microscopic haematuria on more than 2 consecutive days
II	Macroscopic haematuria
III	Macroscopic haematuria with clots
IV	Macroscopic haematuria with clots and impaired renal functions secondary to urinary tract obstruction

Continuous bladder irrigation was initiated with 0.9 % normal saline. However, there was no significant improvement. The patient got temporary relief in cystitis related symptoms with phenazopyridine (pyridium) tablets, urine alkalinizing agents and anti-muscarinic drugs. Immunosuppression was rapidly reduced to the minimal possible level in view of suspicion of ongoing infection. A few days later, qualitative PCR from serum as well as from urine came positive for adenovirus while PCR for cytomegalovirus, BK polyoma

Fig. 3 NCCT KUB showing thickened and inflamed bladder wall

Fig. 4 Sequential samples of urine in a–d shows resolution of hematuria after starting ribavirin

virus and herpes simplex virus were negative. Subsequently, quantitative PCR was also done from serum and urine samples which showed 600 copies/mL and was started on capsule ribavirin with a dose of 20 mg/kg in two divided doses. After 7 days of starting ribavirin, hematuria and dysuria improved significantly (Fig. 4). He completed 4 weeks of therapy with ribavirin which was subsequently stopped. The repeat urine microscopic examination was also within normal limits. The patient is under follow up with complete reversal of LUTS and hematuria.

Discussion

Post transplant hemorrhagic cystitis is one of the challenging side effects faced by transplant teams and urologists. A wide variety of causal factors can give rise to post-

transplant hemorrhagic cystitis (PTHC) as these patients are on various immunosuppressive medications for prevention/therapy of GVHD. The incidence of PTHC among the BMT recipients ranges from 6.5 to 52 % [1, 2]. It is characterized by the classical symptoms of lower urinary tract symptoms like dysuria, haematuria, urgency and increased frequency. For etiological purposes, PTHC has been divided into two categories-infective and non-infective. Non-infective causes include radiation related, chemotherapy induced, GVHD related or as an autoimmune phenomenon. While common infective agents in this setting are bacterial infections like *E. coli* and *Klebsiella pneumoniae*, we must also consider the possibility of opportunistic bacterial/viral organisms as invariably all patients are immunocompromised. In our patient work up for bacterial pathogen, CMV, polyoma virus, HSV were negative, hence the possibility of adenovirus HC was kept

Table 3 Methods/drugs used in hemorrhagic cystitis

Drugs	Route	Class
Cidofovir	Intravenous, local (intravesical)	Antiviral (nucleotide group)
Ribavirin	Intravenous, oral	Antiviral (nucleoside group)
Vidarabine	Intravenous	Antiviral (nucleoside group)
Hyperbaric oxygen therapy	Local (intravesical)	–
Amino caproic acid	Local (intravesical)	Anti-fibrinolysis
Carboprost	Local (intravesical)	Prostaglandin
Donor lymphocyte infusion	Intravenous	Immunotherapy

which was proved by the subsequent urine and serum PCR reports.

Adenovirus infection in the patients of bone marrow transplantation (BMT) can prove to be very fatal. Adenovirus infection in BMT patients can have a spectrum of presentation ranging from just an asymptomatic viral excretion to deadly disease manifestations like fulminant hepatitis, interstitial pneumonia, pancreatitis, gastroenteritis etc. In the series of 2889 adult BMT recipients studied by Alberto et al., 9 patients had asymptomatic viruria and 76 patients had symptomatic infections. HC was the third most common infection caused by adenovirus after upper respiratory tract infections and enteritis in this study [3]. Hale et al. reported HC as the most common manifestation followed by gastroenteritis and pneumonia in his study on 206 pediatric post-BMT patients. In this series, it was found that among the patients who develop adenovirus infections, acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) were the two most common underlying diseases. Serotype analysis was done on five patients and serotype 11 was found to be the most common isolate. Unrelated donor and total body irradiation (TBI) were the two independent risk factors found in this study [4]. In most series, HC is commonly caused by adenovirus subgroup B and serotype 11 [5]. Commonly, adenovirus infection has been documented in the first 100 days of post-BMT period [5, 6]. However, like our case, there are reports when patients have acquired adenovirus infection after 100 days post-BMT [7]. Regarding the associated risk factors involved in acquiring adenovirus infections are type of transplant (allogeneic vs autologous), history of aGVHD, use of immunosuppressive drugs, use of conditioning regimen containing cyclophosphamide, fludarabine or TBI, younger age group, asymptomatic viremia, unrelated donor, adenovirus antibody status of donor, T cell depletion of stem cell harvest [6, 8–11].

Treatment strategies for HC varies in different parts of the world according to the availability of specific drugs (Table 3). Conventional antiviral drugs, especially nucleoside analogues (acyclovir, valacyclovir) are not routinely effective in the treatment of adenovirus related diseases due to the inherent property of adenovirus being deficient in viral

kinases (unlike herpes and CMV group of viruses), thereby making themselves insensitive to the nucleoside analogue antiviral drugs. Cases of vidarabine being effective in adenovirus related HC have been reported in the past, but with variable results [12]. In contrast, nucleotide analogues like cidofovir requires two-staged phosphorylation with the help of monophosphate kinase and pyruvate kinase to form active metabolite which selectively inhibits viral DNA polymerase. Presently cidofovir is FDA approved for CMV retinitis in HIV patients only, however many reports of this broad spectrum antiviral drug have shown its efficacy in adenovirus and related infections [13, 14]. Lindemans et al. proposed algorithm to treat adenovirus infection and disease based on risk categorization, viral load, and failure to respond to pre-emptive treatment. The recommended dose of cidofovir is 1 mg/kg/day (along with probenecid and hyper hydration) thrice a week [13]. In severe cases, intra-vesical instillation of cidofovir has been used successfully. However, cidofovir is not available in many parts of the world therefore, other antivirals have been tried for the treatment of adenoviral infections. Amongst these, ribavirin (nucleoside analogue) is found to be the next most efficient drug [15]. English literature review shows variable results of treatment with ribavirin in various studies [3, 16–18]. The majority of the published literature reports intravenous use of ribavirin as therapy for adenoviral infections. However, in our country, neither cidofovir nor I.V. formulation of ribavirin are not available. Hence, in this case we started oral ribavirin with successful treatment of PTHC. Individual cases of successful treatment of HC with intra-vesical instillation of E-amino caproic acid and prostaglandins have also been reported in literature [19, 20]. Recently a new drug named Brincidofovir has been found efficacious against adenovirus related infections. Currently this drug is in phase III, multicentered study trial and likely to be approved in near future [21].

Conclusion

Polyoma group of viruses is commonly considered as the main pathogen causing hemorrhagic cystitis in organ transplant recipients. In routine practice apart from CMV

virus, most of the transplant centres in developing countries do not test for the other viruses like adenovirus and herpes virus. This case, however highlights the importance of these less common but important group of viruses which must be suspected once the common etiological workup in negative. At the same time it must be emphasized that at present no standard guidelines are drafted regarding treatment of adenovirus related HC and according to availability of antiviral drugs treatment decisions may vary in different parts of the world.

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