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Selective Vesical Artery Embolization in Refractory BK Virus Hemorrhagic Cystitis

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Abstract

In hematopoietic stem cell transplantation (HSCT) recipients, BK virus-related hemorrhagic cystitis is a well-known complication. It increases the risk of death and morbidity of HSCT recipients with simultaneous increase in healthcare cost burden, as a result of prolonged hospital admissions. There are many conservative therapeutic strategies available for the treatment that are effective in treatment of milder forms of hemorrhagic cystitis. Vesical artery embolization is one of the nonsurgical bailout procedure in patient's refractory to medical therapy with added advantage of avoidance of high-risk definitive surgical procedure of cystectomy or urinary diversion in these critical immunosuppressed patients.

Keywords
- hematopoietic stem cell transplantation
- BK virus
- hemorrhagic cystitis

Introduction

In hematopoietic stem cell transplantation (HSCT) recipients, BK virus related hemorrhagic cystitis (HC) is a well-known complication. It increases the risk of death and morbidity of HSCT recipients with simultaneous increase in healthcare cost burden, as a result of prolonged hospital admissions. There are many conservative therapeutic strategies available for the treatment which are effective in treatment of milder forms of hemorrhagic cystitis. Vesical artery embolization is one of the non-surgical bail out procedure in patient's refractory to medical therapy with added advantage of avoidance of high-risk definitive surgical procedure of cystectomy or urinary diversion in these critical immunosuppressed patients.

Among 100 patients treated in our hospital by hematopoietic stem cell transplantation (HSCT, 5 patients [3 male/2 female], aged 5–45 years, mean: 31.6 years) with refractory hemorrhagic cystitis (HC) were treated with vesical artery embolization (►**Table 1**). All the patients underwent allogeneic (haploidentical) transplantation at our hospital with cyclophosphamide used for preconditioning. All patients had BK virus (urine BKV load $>10^7$ gEq/mL) at the time of bleeding with associated thrombocytopenia (mean platelet count: 20,000/µL blood). Conservative treatment for bladder bleeding in the form of hydration, frequent blood transfusion, continuous bladder irrigation, urine alkalinization, and cystoscopic clot evacuation was given to each patient; however, significant bladder bleeding continued in these patients and it was decided in multidisciplinary board to go ahead with vesical artery embolization.

Transcatheter vesical artery embolization was performed through femoral access. A 5-French Cobra catheter (Cook, Bloomington, Indiana, United States) was used to cannulate contralateral internal iliac artery, and ipsilateral iliac artery was cannulated with Sim 1/Sim 2 catheter (Cook, Bloomington, Indiana, United States) through same arterial access. Then, the further angiography of vesical arteries was performed by superselective catheterization with a 2.7 French microcatheter (Progreat Terumo, Tokyo, Japan). Bilateral superior vesical artery embolization was performed in all patients (100%) with bilateral inferior vesical artery

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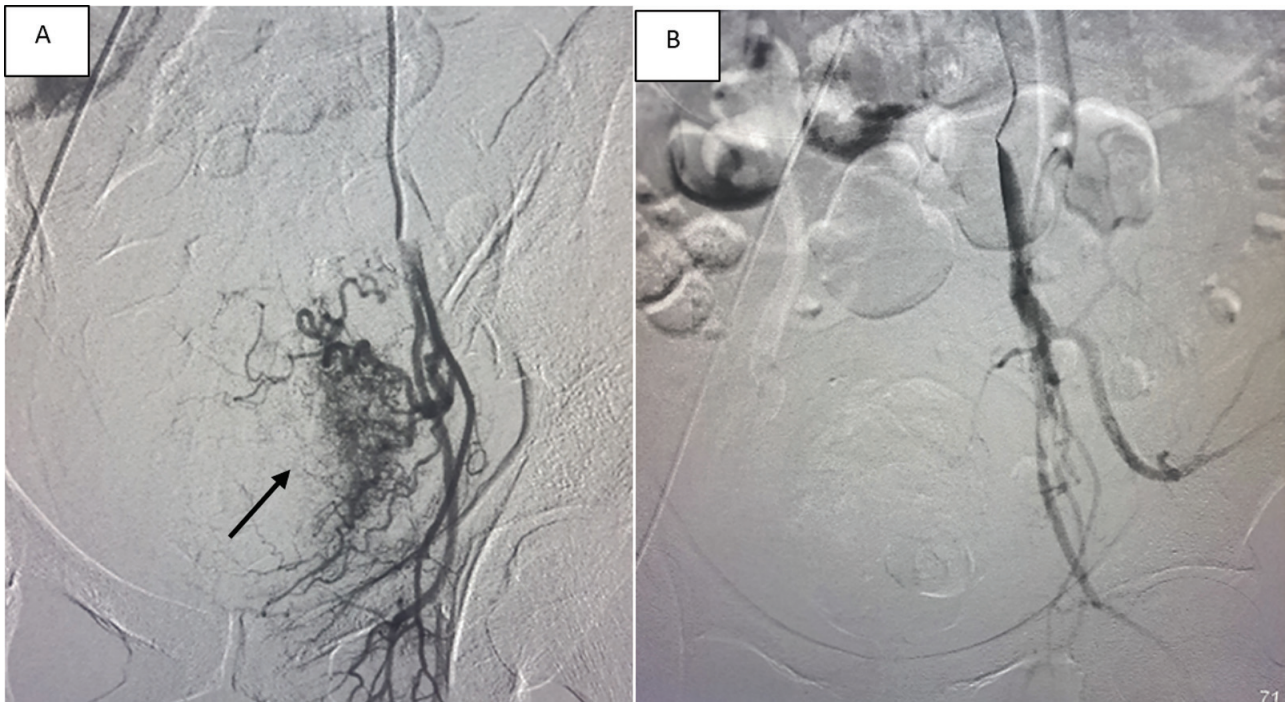

Fig. 1 A 35-year-old woman with hemorrhagic cystitis. **(A)** Angiogram image of left internal iliac artery showing marked bladder wall hypervascularity and abnormal blush. **(B)** Post selective vesical artery embolization showing absence of abnormal blush.

embolization in one patient (20%). Bladder neovascularity, abnormal blush, and capillary staining were the common findings before embolization (►**Figs. 1–3**). Embolization was done with 300 to 500 microns polyvinyl alcohol (PVA) particles diluted with contrast/saline, till there was occlusion of the vesical hypervascularity. Continued bladder irrigation was continued for 48 hours after the procedure.

After embolization treatment, all five patients (100%) showed marked improvement in clinical symptoms. Three patients (60%) (after one session, after two sessions) achieved complete response, their hematuria, and symptoms ceased completely with no further requirement of blood transfusion or cystoscopic clot evacuation. Two patients obtained partial response to embolization treatment (macroscopic hematuria reappeared after 48 hours with bladder clot formation); however, instead of second session of embolization formalin bladder wash was given during cystoscopic clot evacuation with further resolution of symptoms.

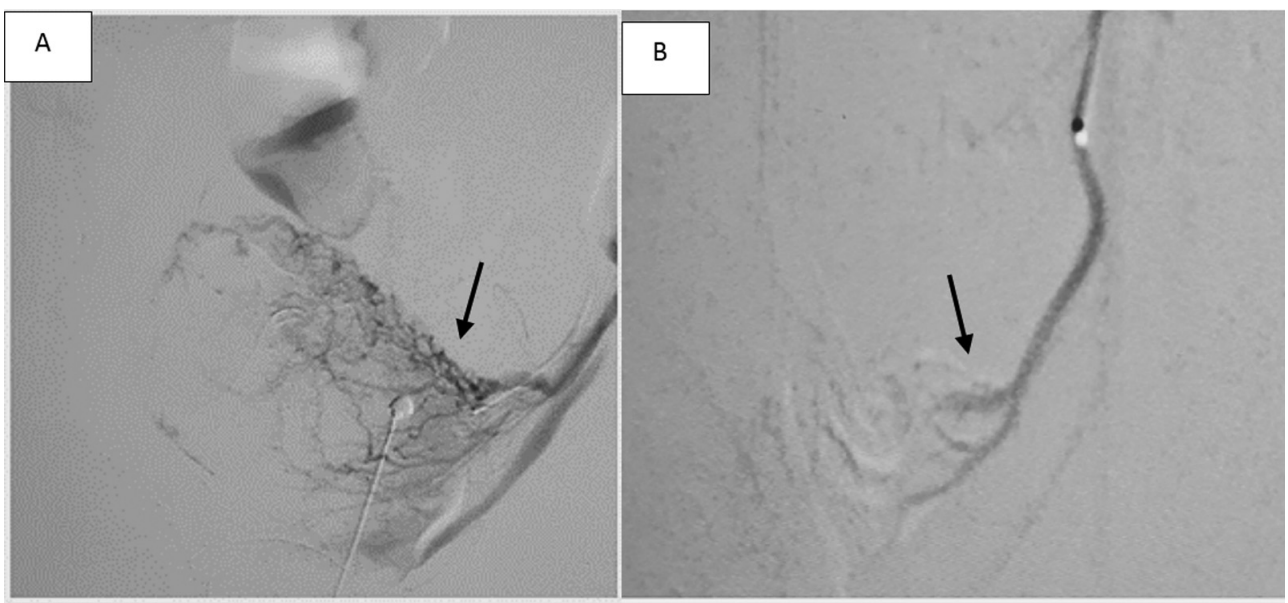

Fig. 2 A 5-year-old male child with hemorrhagic cystitis. **(A)** Angiogram image of selective left vesical artery showing mild bladder wall hypervascularity, capillary staining, and abnormal blush. **(B)** Post selective left vesical artery embolization showing absence of abnormal blush.

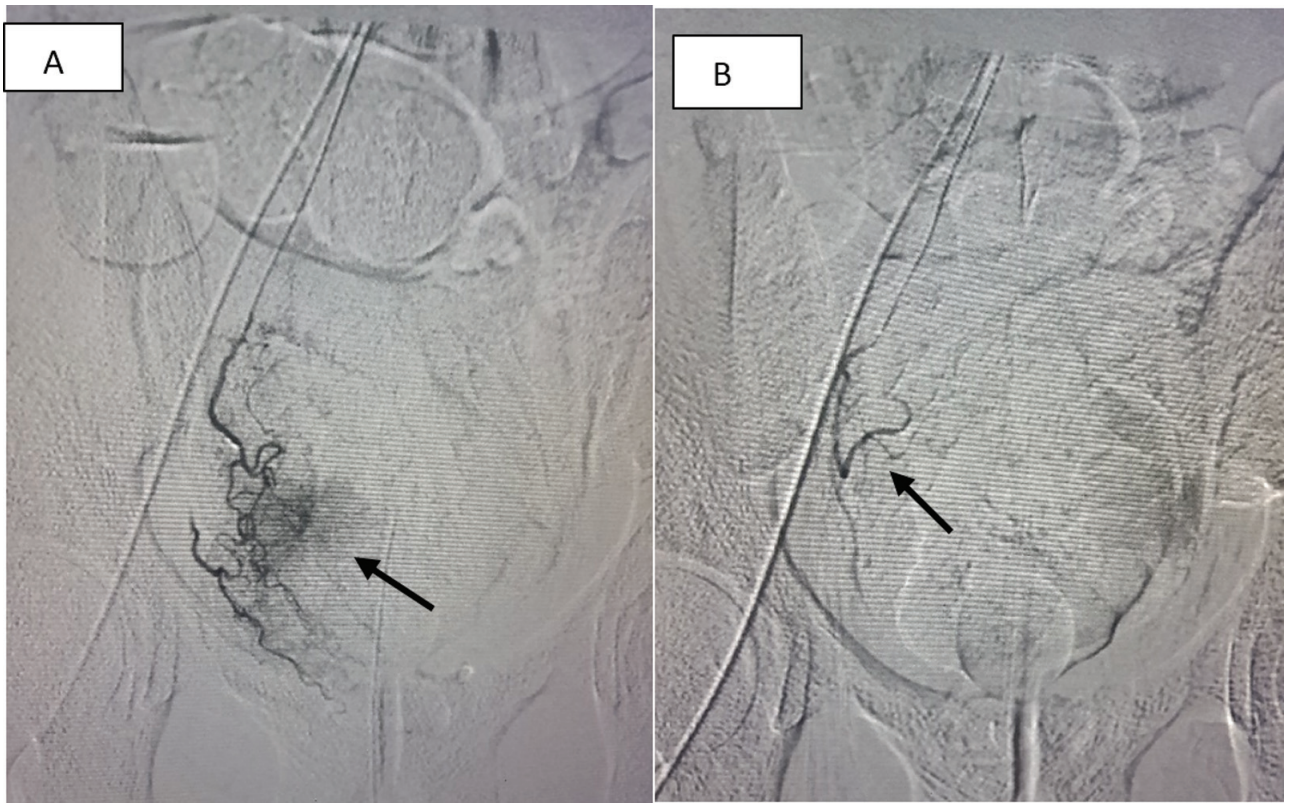

Fig. 3 A 38-year-old man with hemorrhagic cystitis. **(A)** Angiographic image of selective right vesical artery angiogram showing mild bladder wall hypervascularity, and abnormal blush. **(B)** Post selective right vesical artery embolization showing absence of abnormal blush.

Table 1 Patient data

Patient	Age/sex	Disease	HSCT type	HC grade	HC onset (days)	HC duration (days)	Response	Number of embolizing sessions
1	35/F	ALL	Haplo	3	40	20	Complete	2
2	35/M	ALL	Haplo	3	45	22	Complete	1
3	45/F	MDS	Haplo	3	38	14	Complete	1
4	5/M	ALL	Haplo	3	40	16	Partial	1
5	38/M	MDS	Haplo	3	36	28	Partial	1

Abbreviations: ALL, acute lymphocytic leukemia; HC, hemorrhagic cystitis; Haplo, haploidentical; HSCT, hematopoietic stem cell transplantation; MDS, myelodysplastic syndrome.

There was a mean follow-up of 11 months (range, 4–40). The mean interval for the onset of HC after HSCT was 40 ± 10.0 days, and mean duration of hematuria before embolization was 10 days. No major procedure-related complications were noted except for low-grade fever and mild pelvic pain in two patients that resolved in 24 hours.

Discussion

The reported incidence[1] of post-HSCT BKV-related HC is highly variable among adults (7–54%) and children (8–25%). BKV is a human polyoma virus that is acquired in childhood and remains latent in genitourinary system. Higher grade viremia occurs in immunosuppressed patients and following engraftment in hematopoietic stem cell transplant recipients. BKV-related HC is commonly seen in allogeneic HSCT recipient as alloimmunity plays a crucial role in pathogenesis of BKV-related HC in these patients. The other risk factors associated with BKV-related HC include older age of transplant and associated cytopenias, transplant in unrelated donor, graft versus host disease, myeloablative conditioning (cyclophosphamide therapy, use of busulfan and total-body irradiation), and high virus load (BKV, cytomegalovirus).[2]

Etiopathogenesis[3] of HC involves bladder mucosal damage caused by chemotherapeutic agents and irradiation, followed by BKV replication under the suppressed immune status with final phase comprising of an inflammatory response of the recovering host immunity against activated

BK leading to development of microscopic or gross hematuria accompanied by lower urinary tract symptoms of dysuria and suprapubic pain. The severity is graded[4] as microscopic hematuria (grade 1), macroscopic hematuria (grade 2), and hematuria with clots requiring transfusion products (grade 3) and with associated renal dysfunction as grade 4.

Most cases are mild and self-limited and can be treated with conservative therapies. In severe cases, medical management includes hyper hydration and continuous bladder irrigation (prevents clot formation). Intravesical instillation[1] of agents like alum, formalin, estrogens, and prostaglandin or sodium hyaluronate has been tried that act by reducing bleeding by vasoconstriction and decreased capillary permeability. Other treatment options available are gradual reduction of immunosuppression regimen; however, it is associated with higher incidence of acute and chronic rejection. Hyperbaric oxygen therapy[1] has been associated with a few successes. Use of antiviral drugs cidofovir, brincidofovir, and leflunomide targets the virus replication and can be applied as treatment options.

Surgical procedures[5] of urinary diversion by bilateral percutaneous nephrostomies (prevents urinary urokinase in urine from reaching bladder), open cystotomy with urinary diversion, and cystectomy with or without the reconstruction of a neobladder have been used, but are associated with high morbidity and mortality.

Vesical artery embolization is a minimally invasive treatment for bladder bleeding and has been used in controlling intractable tumoral bleed[6] due to bladder/prostatic cancer and bleed secondary to chemotherapy/radiation cystitis. It has been used for the management of BKV HC[7] with good clinical outcomes and without any serious short-term or long-term side effects. In the present study, hematuria initially regressed in all five patients within 48 hours after bilateral superior vesical artery embolization with recurrence in three patients out of which one was completely controlled with second session (embolization of bilateral inferior vesical arteries) and two other with formalin bladder wash. The first session of bilateral superior vesical arteries was done with permanent embolizing agents (PVA particles, size 300–500 microns). Both superior and inferior vesical arteries were not embolized in one session keeping in mind risk of bladder necrosis due to rapid occlusion of all vasculature and providing time for bladder repair. Temporary embolizing agent Gelfoam was used for inferior vesical artery occlusion in one patient. Some studies[8] state that temporary embolization is enough to achieve satisfactory hemostasis because one of the etiologies for bladder bleeding is immunosuppression and it gets relieved by immune reconstitution. But we used permanent embolizing agents of PVA size 300 to 500 microns for superior vesical arteries in our patients and achieved good results consistent with other studies.[8,9] The risk of bladder necrosis is minimal due to abundant collateral supply to the bladder. Use of smaller size particles (below 200 microns) should be avoided to prevent bladder necrosis.[9] Two of our patients who developed partial response were not taken up for second embolization session as they responded to formalin bladder wash after clot evacuation during cystoscopy. Primary straightforward use of formalin or alum bladder wash is avoided as there are chances of bladder necrosis and infection. One of the two patients was in pediatric age group and there is limited literature to support embolizing all four bladder arteries in these patients.[10] The other patient developed procedure unrelated transplant complications (pulmonary infection) and in that patient it was decided to do formalin wash during cystoscopic clot evacuation and delay the second embolizing session. Thus, in all cases vesical artery embolization helped in avoiding more invasive procedures of urinary diversion.

Conclusion

Management of BKV-related HC in stem cell transplant recipients is a challenging task. Selective vesical artery embolization is a safe and effective treatment option in patients who are not responding to medical management, and can lead to marked improvement in transplant outcomes.

Conflict of Interest
None declared.

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