Two Cases of Intractable Radiation-Induced Hemorrhagic Cystitis Treated with Transcatheter Embolization

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Radiation-induced hemorrhagic cystitis is a late complication of radiotherapy, and in rare cases, refractory. Refractory bleeding may not be resolved by transurethral electrocoagulation (TUEC) or hyperbaric oxygen (HBO) therapy and requires transcatheter arterial embolization (TAE) or urinary diversion. Here, we report two cases of radiation-induced hemorrhagic cystitis successfully treated with TAE. Case 1 was a 61-year-old man who underwent total prostatectomy for prostate cancer followed by salvage radiation therapy. The patient developed radiation-induced hemorrhagic cystitis 2 years and 3 months after radiotherapy. After no improvement with TUEC and HBO, TAE was performed. Case 2 was a 78-year-old man who underwent total prostatectomy followed by salvage radiation therapy and developed radiation-induced hemorrhagic cystitis 12 years later. TAE was performed after no improvement with HBO. TAE proved successful in both patients, and there was no relapse. TAE is a potential treatment option for refractory radiation-induced hemorrhagic cystitis.

Key words: Transcatheter embolization, Radiation-induced hemorrhagic cystitis, Hyperbaric oxygen

INTRODUCTION

Radiation-induced hemorrhagic cystitis is a late complication of radiotherapy for malignant tumors that typically develops at least three months after treatment. However, cases in which the condition has developed 10 or more years after radiotherapy have been reported [1]. Refractory hemorrhagic cystitis is treated with a range of therapies, including transurethral electrocoagulation (TUEC), transcatheter arterial embolization (TAE), hyperbaric oxygen (HBO) therapy, and urinary diversion [2–4]. Nevertheless, there is currently no established treatment for the disorder. Though a few reports have examined TAE in the treatment of hemorrhagic cystitis [5, 6], however, there is a relative scarcity of reports on TAE in the treatment of radiation-induced hemorrhagic cystitis caused by salvage radiation therapy after total prostatectomy for prostate cancer. Additionally, the effects of TAE on urinary function in such cases remain unknown. Herein, we report our experience with two cases of treatment-refractory radiation-induced hemorrhagic cystitis that eventually responded to TAE.

Case 1

The patient was a 61-year-old man who underwent robot-assisted laparoscopic prostatectomy for prostate cancer at the age of 57 years and salvage radiation therapy (66 Gy/33 fr) 6 months after the surgery. The patient experienced occasional incontinence following surgery. The patient presented with gross hematuria 2 years and 3 months after radiotherapy. His hemoglobin level was 3.0 gm/dL. Therefore, he was transfused with eight units of blood. TUEC was performed after continuous bladder irrigation failed to control the bleeding. Erythema and petechial bleeding across the entire bladder but concentrated in the trigone were noted; the bleeding was stopped in the same areas. Simultaneously, we performed bladder biopsy; histological features revealed urinary cystitis. Based on the above, a diagnosis of radiation-induced hemorrhagic cystitis was reached. Although controlled temporarily, the bleeding reappeared and TUEC was repeated. Then, 23 sessions of HBO therapy were performed. Hematuria was poorly controlled despite these efforts, and TAE was performed by a radiologist. A 4 Fr sheath was inserted into the right common femoral artery and a cannula was inserted into the right internal iliac artery. Using a combination of a 0.014-inch microguidewire and a 1.9/2.8 Fr microcatheter, a vessel common to the superior vesical artery and inferior vesical artery was selected and embolization was performed (Fig. 1a). Next, the left inferior vesical artery was embolized selectively in a similar manner (Fig. 1b). Serescue® (Astellas Pharma Inc., Japan) was used as the embolization agent. Hematuria stopped completely overnight, and the patient was discharged nine days after TAE. Three years have elapsed since

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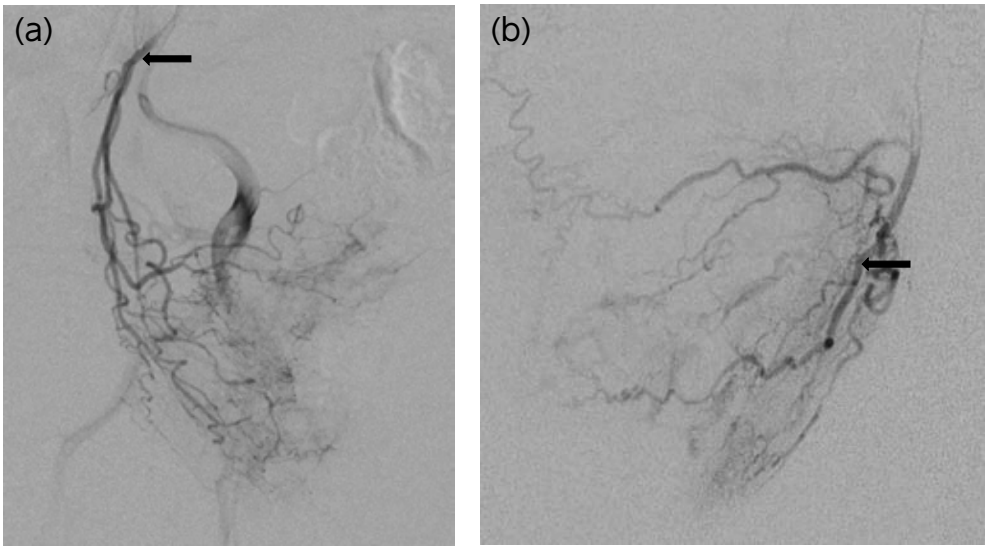

Fig. 1 A 61-year-old man with radiation-induced hemorrhagic cystitis after salvage radiation therapy (Case 1). (a) Angiogram of the right internal iliac artery region. Embolization was performed in a vessel common to the superior vesical artery and inferior vesical artery (black arrow). (b) Angiogram of the left internal iliac artery region. Due to extravasation of contrast from the left inferior vesical artery, embolization was only performed in the left inferior vesical artery (black arrow).

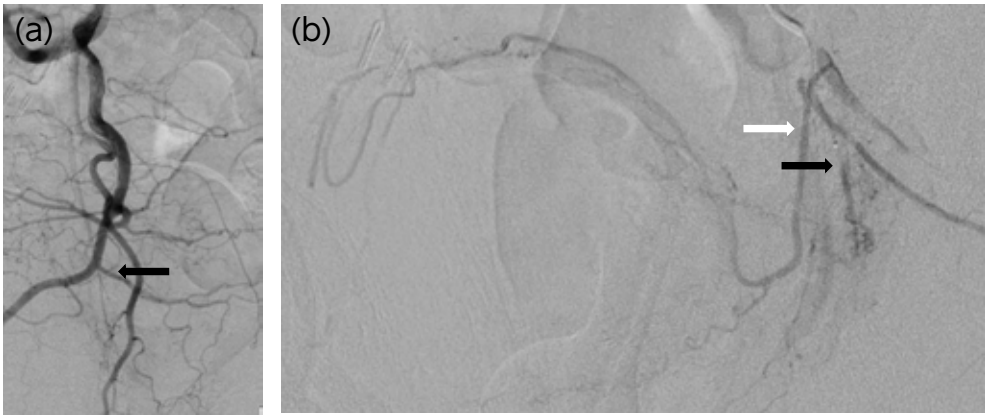

Fig. 2 A 78-year-old man with radiation-induced hemorrhagic cystitis after salvage radiation therapy (Case 2). (a) Angiogram of the right internal iliac artery region. Embolization was only performed in the right inferior vesical artery (black arrow). (b) Angiogram of the left internal iliac artery region. Embolization was performed in turns in the left superior vesical artery (white arrow) and left inferior vesical artery (black arrow).

the TAE, and there has been no recurrence of gross hematuria. However, urinary incontinence has worsened since TAE, and the patient is using a penile clamping device.

Case 2

The patient was a 78-year-old man who underwent laparoscopic radical prostatectomy for prostate cancer at the age of 67 years followed by postoperative salvage radiation therapy (66 Gy/33 fr). The patient was on oral warfarin potassium because of a history of atrial fibrillation. From year three after the radiotherapy onward, the patient occasionally presented with gross hematuria. Twelve years after the radiotherapy, the patient presented with gross hematuria again; a diagnosis of radiation-induced hemorrhagic cystitis was reached because the urine cytology was negative and no visible abnormality in the urinary tract was noted on computed tomography. Warfarin potassium was suspended, and 25 sessions of HBO therapy were performed followed by TUEC. Despite these efforts, the hematuria remained poorly controlled, and TAE was performed by a radiologist. A 4 Fr sheath was inserted into the right common femoral artery and a cannula was inserted into the right internal iliac artery. Next, a 1.7/2.7 microcatheter was advanced to the inferior vesical artery and the inferior vesical artery was selectively embolized (Fig. 2a). On the left side, the superior vesical artery and inferior vesical artery were each embolized in turn (Fig. 2b). Again, Serescue® (Astellas Pharma Inc., Japan) was used as the embolization agent. Hematuria stopped completely overnight, and oral warfarin potassium was resumed with no recurrence of hematuria. The patient was discharged 29 days after TAE. However, he required indwelling urethral catheter owing to the development of severe dysuria after TAE. Three years have elapsed since TAE, and there has been no recurrence of gross

hematuria.

DISCUSSION

Hemorrhagic cystitis is caused by drugs such as cyclophosphamide and ifosfamide, radiotherapy, viral infection, and systemic disorders [2]. The incidence of hemorrhagic cystitis after radiotherapy for prostate cancer is 13% to 28% when microscopic hematuria is included [7, 8], and only 6.9% of patients with radiation-induced hemorrhagic cystitis require TAE [3].

Intravesical treatments for cases of refractory hemorrhagic cystitis include TUEC and irrigation with alum, silver nitrate, prostaglandin, and an aluminum hydroxide-magnesium mixture [4], although the efficacy of these treatments is limited, and bleeding often reappears. Second-line treatments for refractory hemorrhagic cystitis are irrigation with formalin, HBO, and TAE. Regardless of the treatment used, urinary tract diversion is often performed in non-responsive cases, despite it being the most invasive of all therapies. Intravesical irrigation with formalin is also an extremely powerful treatment that is associated with risks such as bladder fibrosis, decreased bladder capacity, ureteral and urethral strictures, and hydronephrosis [2].

HBO therapy was used in the two cases described in this report. It increases the concentration of oxygen dissolved in plasma, thereby improving peripheral hypoxia, causing angiogenesis and fibroblast growth, and promoting the formation of granulation tissue and tissue healing in the bladder mucosa [4, 9–11]. In a single HBO session, the patient is exposed to 100% oxygen at 1.5 to 3 atmospheres absolute for 60 to 120 min. HBO therapy has been reported to be successful after fewer than 10 sessions [2], while 20 to 40 sessions have been reported to afford therapeutic benefits in 80% to 90% of patients [10]. A certain proportion of patients are unresponsive regardless of the treatment administered, although the underlying reason why some cases of radiation-induced cystitis are unresponsive to HBO therapy remains unknown [10]. Patient 1 received HBO therapy after the second occurrence of hematuria, although it may have been more beneficial to administer HBO sooner after the first urethral treatment. At present, insufficient evidence is available to determine the appropriate timing and number of sessions of HBO therapy.

TAE for radiation-induced hemorrhagic cystitis was first described by Hald *et al.* in 1974 [12]. Recent reports describe a wide range of success rates, from 40% to 100%, of TAE for radiation-induced hemorrhagic cystitis [5, 6]. Mohan *et al.* reported a sustained response in 78% of patients during a mean follow-up period of 14.5 months [6]. The main complications of TAE are gluteal pain, fever, nausea, vomiting, and pain in the back of the thigh [13]. Comploj *et al.* observed mild complications in just 20% of patients and no clinically significant complications [5], and Mohan *et al.* reported no effect on sexual or bladder function because of treatment with selective embolization for intractable hematuria secondary to hemorrhagic cystitis [6]. In both cases described in this report, TAE was successful and there was no subsequent recurrence. However, dysuria was observed after TAE in both patients, and Patient 1 was also unable to maintain continence. In past reports of radiation-induced hemorrhagic cystitis, the proportion of patients with radiation-induced hemorrhagic cystitis associated with salvage radiation after total prostatectomy and their degree of dysuria before TAE were unknown. In our two cases, urinary function may have been preserved by being more selective about the site of embolization, although selective embolization was not possible because the bleeding point was unknown. In addition, the fact that urinary incontinence and dysuria were already present after total prostatectomy probably contributed to the problems with urinary function encountered after TAE. Therefore, when seeking consent for TAE, patients should be fully informed about post-TAE deterioration of urinary function if dysuria is present before the procedure.

CONCLUSION

We described our experience of treating two cases of radiation-induced hemorrhagic cystitis in which bleeding was eventually controlled by performing TAE. Our success with TAE avoided more invasive treatments such as total cystectomy and urinary tract diversion and demonstrated that TAE is an effective treatment option for radiation-induced hemorrhagic cystitis.

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