INTRACTABLE HEMATURIA IN BLADDER CANCER WITH UNILATERAL HIGH GRADE VESICOURETERAL REFLUX: A CONSERVATIVE APPROACH USING INTRAVESICAL FORMALDEHYDE INSTILLATION

[1] Reginald Rustandi, [2]Rachmat Budi Santoso, [2]Edward Usfie Harahap, [2]Ikhlas Arief Bramono.

[1] Department of Urology, Faculty of Medicine/Universitas Indonesia, Cipto Mangunkusumo Hospital, Jakarta.
[2] Division of Urology, Indonesia National Cancer - Dharmais Cancer Hospital, Jakarta.

ABSTRACT

Objective: *This study aims to report a case of intractable hematuria in a patient with bladder cancer after radiotherapy.* ***Case(s) Presentation:*** *This case reported a 41-year-old male with urothelial carcinoma of bladder who came to our hospital hematuria symptoms that arised four months after radiotherapy session. The patient was admitted several times with intractable hematuria along with low levels of hemoglobin, and diagnosed with cystitis radiation.* ***Discussion:*** *Voiding cystourethrogram (VCUG) showed unilateral high grade vesicoureteral reflux (VUR). The patient showed no sign of improvement after transarterial embolization (TAE), radiation, and high-dose of steroids. However, the symptoms finally resoluted after formaldehyde instillation.* ***Conclusion:*** *Patients with a history of bladder cancer who develop hematuria after radiotherapy should be evaluated promptly to exclude the possibility of recurrent disease. The administration of formaldehyde instillation could lower the symptoms of hematuria and maintain hemoglobin levels.*

Keywords: *Intractabel hematuria, formaldehyde, bladder cancer.*

ABSTRAK

Tujuan: *Penelitian ini bertujuan untuk melaporkan kasus hematuria yang sulit diatasi pada pasien dengan kanker kandung kemih setelah radioterapi.* ***Presentasi Kasus:*** *Seorang pria berusia 41 tahun datang ke rumah sakit kami dengan gejala karsinoma urotelial kandung kemih dan hematuria yang muncul empat bulan setelah sesi radioterapi. Pasien dirawat beberapa kali dengan hematuria yang sulit diatasi dan kadar hemoglobin rendah disertaisistitis radiasi.* ***Diskusi:*** *Voiding cystourethrogram (VCUG) menunjukkan refluks vesikoureteral (VUR) unilateral tingkat tinggi. Pasien tidak menunjukkan tanda-tanda perbaikan setelah embolisasi transarterial (TAE), radiasi, dan steroid dosis tinggi. Namun, gejalanya akhirnya mereda setelah pemberian formaldehida.* ***Simpulan:****Pasien dengan riwayat kanker kandung kemih yang mengalami hematuria setelah radioterapi harus segera dievaluasi untuk menyingkirkan kemungkinan penyakit berulang. Pemberian formaldehida secara bertahap dapat menurunkan gejala hematuria dan mempertahankan kadar hemoglobin.*

Kata kunci: *Hematuria yang sulit diatasi, formaldehida, kanker kandung kemih.*

Correspondence: Reginald Rustandi; c/o: Department of Urology, Faculty of Medicine/Universitas Indonesia, Cipto Mangunkusumo Hospital, Jalan Diponegoro No. 71, Jakarta 10320, Indonesia. Email: regirustandi@gmail.com.

INTRODUCTION

Bladder cancer is one of the most common urinary tract cancer worldwide. Based on the latest GLOBOCAN data, it accounts for 3% of global cancer diagnoses and is particularly prevalent in the developed world.[1] In 2020, as many as 573.278 new cases of bladder cancer were diagnosed worldwide, and 212.536 deaths due to bladder cancer were recorded.[2]

Unfortunately, a lot of patients with bladder cancer have comorbidities, such as cardiovascular problem, kidney function impairment, respiratory disease, or other age-related comorbidities which make them ineligible to undergone surgery such as radical cystectomy or undergone chemotherapy procedure.[3] Other reason that often make an individual refuse to do surgery is that will impaired their micturition function, disturb their quality of life and the lengthy postoperative bladder training sequence.[4]

Radiotherapy as one of the modalities available for bladder cancer, is one of the available treatment option for bladder cancer patients.

However, it can result in various complications, including radiaton-induced cystitis that often manifests as intractable hematuria.[5] Here we report a case of intractable hematuria in a patient with bladder cancer after radiotherapy.

CASE(S) PRESENTATION

A 41-year-old male patient came to our hospital with painless and recurrent hematuria since 2018. One month prior, a cystoscopy was performed and the patient diagnosed with urothelial carcinoma of bladder after the pathology result came out. The patient then underwent radiotherapy because he refused to do a radical cystectomy He received a total radiation dose of 63 Gy which divided to 35 radiotherapy sessions until December 2022 (the patient received 1.8 Gy dose of radiotherapy in each session).

Four months after completing the radiotherapy session, the patient was admitted several times to our hospital with low levels of hemoglobin. The symptoms of hematuria worsened after radiotherapy, along with blood clotting in his urine, although the patient still able to urinate spontaneously. Some different approaches of hematuria management were performed. First we performed transarterial embolization (TAE). After that, patient were given 10 radiotherapy sessions in two weeks, with 3 Gy dose of radiation in each session, but no sign of improvement. We also gave the patient 5 days of high-dose steroid therapy (5 milligrams, three times daily intravenously), however still no sign of improvement and no improvement in patient's hemoglobin levels (Figure 1).

Next step management of hematuria were taken by performing formaldehyde instillation. However, before the procedure performed, a cystoscopy and voiding cystourethrogram (VCUG) were performed. A 30, 50, 100, 150, and 200 milliliters of contrast instillation were performed. At 50 milliliters, bladder wall were appeared irregular, with no additional shadow, no filling defect, no diverticle, and no vesical stones. Grade IV of left vesicoureteral reflux (VUR) was visible IV during 50 milliliters of contrast instillation, and grade V of left VUR was subsequently visible after 200 milliliters of contrast instillation (Figure 4). Bladder capacity was measured at 200 milliliters.

Due to VUR finding during VCUG, insertion of bilateral ureteral catheter were performed to prevent the reflux of formaldehyde. After ureteral catheter insertion, first instillation of 100 milliliter of 1% formaldehyde were performed through three-way 18-french foley catheter for 30 minutes. After the first instillation, patient said that the hematuria symptoms felt slightly better, although hemoglobin levels were still fluctuating.

Two weeks after, the second formaldehyde instillation were performed. This second instillation were performed using 200 milliliter of 1% formaldehyde for 30 minutes. After instillation procedure completed, ureteral catheter then immediately removed, and followed by drip of 0,9% natrium chloride through 24-french foley catheter. Hematuria symptoms were getting better subsequently (Fig 5a, 5b, and 5c) with hemoglobin levels were remain stable above 8 g/dL.

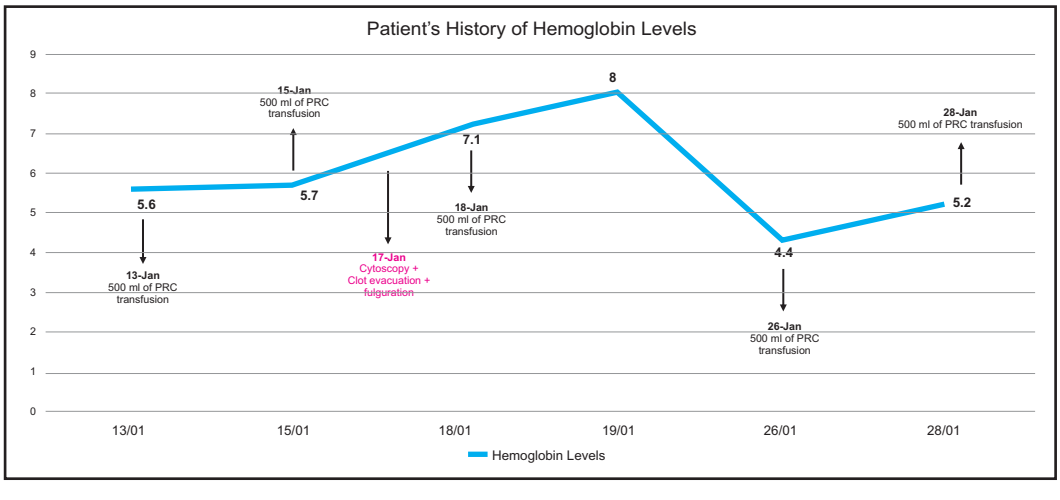

Figure 1. Chart of patient's hemoglobin levels around fulguration period.

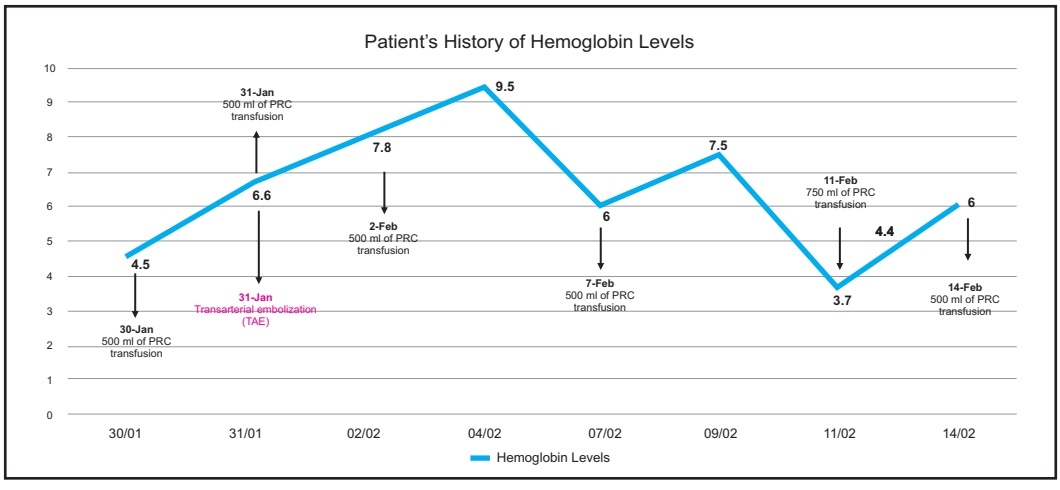

Figure 2. Chart of patient's hemoglobin levels around TAE period.

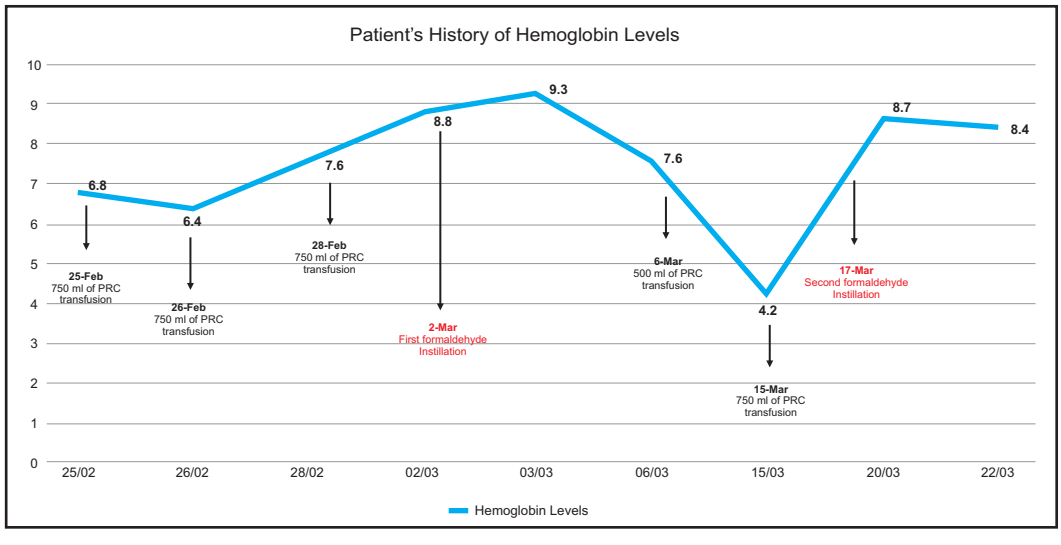

Figure 3. Chart of patient's hemoglobin levels around first and second formaldehyde instillation period.

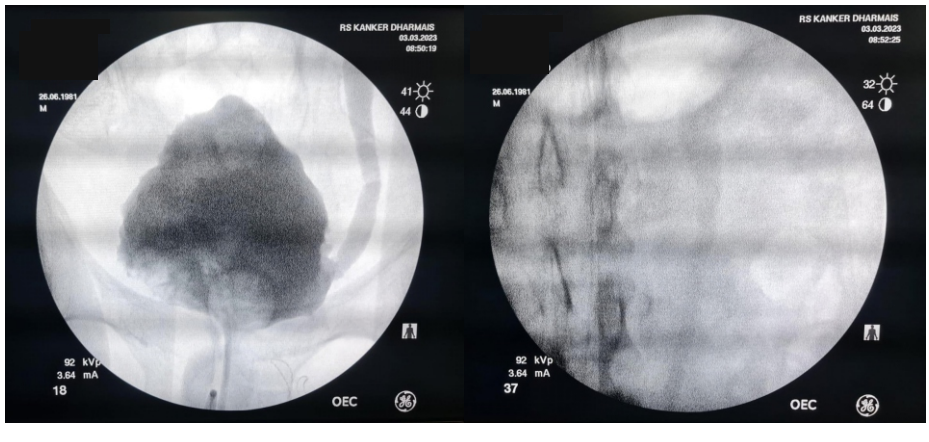

Figure 4. Grade IV left VUR was found during VCUG examination at 50 millilters of contrast instillation.

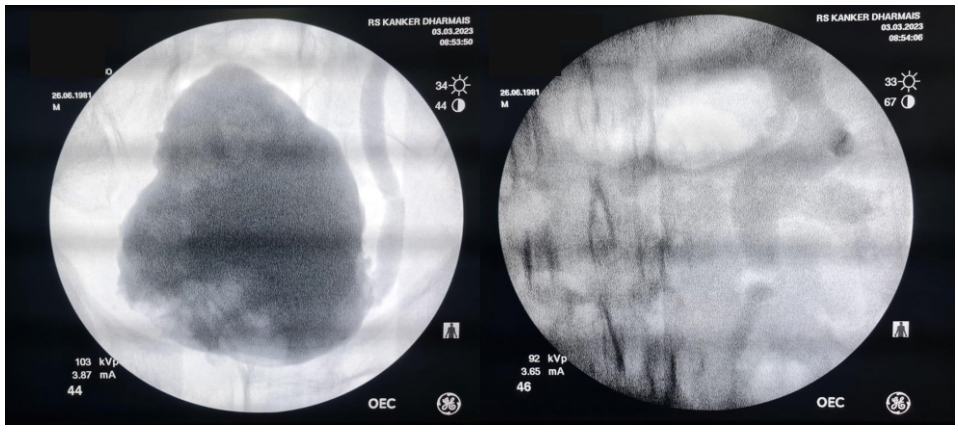

Figure 5. Grade V left VUR was found during VCUG examination at 200 millilters of contrast instillation.

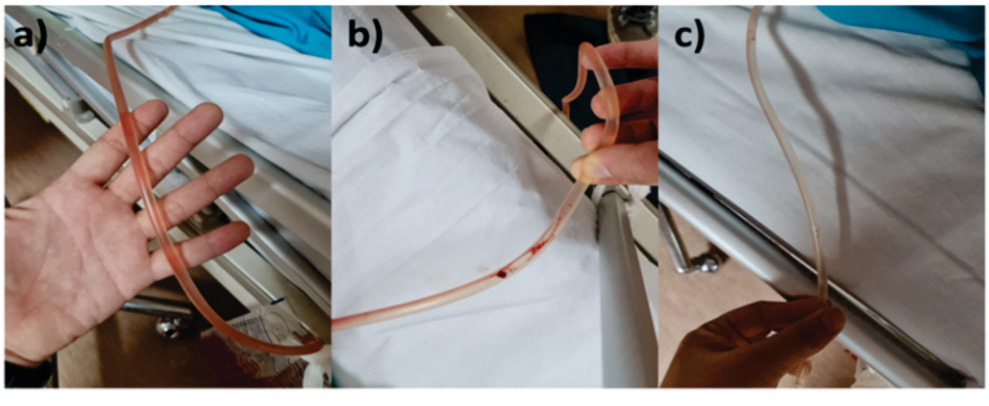

Figure 6. Patient's hematuria symptom was showing positive result after the secong formaldehyde instillation. a) Day 1 after second instillation, b) Day 2 after second instillation, c) Day 3 after second instillation

DISCUSSION

Radiotherapy is a commonly used treatment modality for bladder cancer patients. In terms of radiotherapy as primary therapy, urothelial cancers are substantially more radiosensitive compared to other cancers (e.g. prostate cancer), radiation given at doses of 55 to 65 Gy alone as primary therapy would give a long-term local control rate of around 30% to 40%.[6]

In this case report, reported a patient that was diagnosed with stage II bladder cancer, with comorobidities of hepatitis C and stage 4 chronic kidney disease. This extensive comorbidites condition made him was not eligible to receive cisplatin-based chemotherapy. Moreover, the patient refused to do a radical cystectomy since he was afraid that it might disturb his quality of life. Thus, in line with the 2023 National Comprehensive Cancer Network (NCCN 2023), patient was planned to receive radiotherapy as the primary treatment.[7]

Unfortunately, radiotherapy as primary treatment in bladder cancer can result in various complications, including hematuria. Although only developed in a small proportion of the treated population, radiation therapy given to the bladder cancer patients could lead to radiotherapy-induced hemorrhagic cystitis, which is a potentially devastating side-effect. This can occur long after radiotherapy has ended, ranged from 2 months to 15 years after therapy[8], and affecting roughly 6.5% of patients following radiotherapy in pelvic area.[9]

In this case, the patient developed hematuria four months after completing radiotherapy, with no sign of improvement after TAE, radiation, and high-dose of steroids. However, the symptoms finally resoluted after formaldehyde instillation. Formaldehyde treatment administered intravesically

results in the precipitation of cellular proteins within the bladder. This leads to the closure and fixing of telangiectatic tissue and small capillaries. The use of formalin for the treatment of inoperable bladder carcinoma was initially reported in 1969 by Brown. In a study involving 24 patients with advanced carcinoma who had hematuria and strangury, a 10% formalin solution was infused into their bladder for 15 minutes. Within 1 to 5 days, 22 patients had relieved from hematuria, with an average duration of 4 months, and there were no general complications. As a result, Brown deemed the technique to be both safe and effective.[10]

However, the use of formalin to overcome symptoms of intractable hematuria is no longer common in everyday clinical practice. This could be cause due to a high rate of major complications, such as kidney failure, retroperitoneal fibrosis, a significant decrease in bladder capacity, and intense lower urinary tract symptoms, which can add burden to patient's symptoms and conditions.[11] Moreover, in patient with existing VUR, sudden reflux of formaldehyde could lead to acute kidney failure and potentially resulted in morbidity and mortality.[12] Hence, it was necessary to diagnose the existing VUR in patient with cystoscopy and VCUG before formaldehyde instillation performed.

CONCLUSION

Hematuria after radiotherapy for bladder cancer can be a sign of recurrent disease. Patients with a history of bladder cancer who develop hematuria after radiotherapy should be evaluated promptly to exclude the possibility of recurrent disease. The administration of formaldehyde instillation could lower the symptoms of hematuria and maintain hemoglobin levels. However, further research is needed to investigate the optimal management of patients with hematuria after radiotherapy for bladder cancer, since the adverse event of formaldehyde instillation is notably high in some studies.

REFERENCES

1. Saginala K, Barsouk A, Aluru JS, Rawla P, Padala SA, Barsouk A. Epidemiology of Bladder Cancer. Med Sci (Basel). 2020 Mar 13; 8(1):15.
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021 May;71(3): 209-249.
3. Antoni S, Ferlay J, Soerjomataram I, Znaor A, Jemal A, Bray F. Bladder Cancer Incidence and Mortality: A Global Overview and Recent Trends. Eur Urol. 2017 Jan; 71(1): 96-108.
4. Lavdaniti M, Zyga S. Quality of Life in Elderly Bladder Cancer Patients Following a Cystectomy. Adv Exp Med Biol. 2017; 989: 297-300.
5. Pham A, Ballas LK. Trimodality therapy for bladder cancer: modern management and future directions. Curr Opin Urol. 2019 May; 29(3): 210-215.
6. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology – Bladder Cancer. 2023. Feb 1; 9.
7. Aragon-Ching JB, Werntz RP, Zietman AL, Steinberg GD. Multidisciplinary Management of Muscle-Invasive Bladder Cancer: Current Challenges and Future Directions. Am Soc Clin Oncol Educ Book. 2018 May 23; 38: 307-318.
8. Payne H, Adamson A, Bahl A, Borwell J, Dodds D, Heath C, Huddart R, McMenemin R, Patel P, Peters JL, Thompson A. Chemical- and radiation-induced haemorrhagic cystitis: current treatments and challenges. BJU Int. 2013 Nov;112(7): 885-97.
9. Alesawi AM, El-Hakim A, Zorn KC, Saad F. Radiation-induced hemorrhagic cystitis. Curr Opin Support Palliat Care. 2014 Sep; 8(3): 235-40.
10. Abt D, Bywater M, Engeler DS, Schmid HP. Therapeutic options for intractable hematuria in advanced bladder cancer. Int J Urol. 2013 Jul; 20(7): 651-60.
11. Ghahestani SM, Shakhssalim N. Palliative treatment of intractable hematuria in context of advanced bladder cancer: a systematic review. Urol J. 2009 Summer; 6(3):149-56.
12. Sarnak MJ, Long J, King AJ. Intravesicular formaldehyde instillation and renal complications. Clin Nephrol. 1999 Feb; 51(2): 122-5.