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Aplastic anemia associated with severe hemorrhagic cystitis following radiotherapy for prostate cancer

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Abstract. Hemorrhagic cystitis is a rare complication following radiotherapy for intrapelvic cancer types, including cervical cancer, bladder cancer and prostate cancer. The severity of hemorrhagic cystitis is different in each case, although symptoms improve spontaneously in certain cases, and often significant morbidity requiring numerous interventions occurs. Since no treatment strategy exists with high evidences for such severe hemorrhagic cystitis, urologists have difficulty in solving the bleeding and pain, which the patients suffer. Aplastic anemia is a rare blood disorder, with an incidence reported as 2/1 million individuals annually. Patients have a risk of diffuse bleeding for presentation with anemia, thrombocytopenia and neutropenia. The present report presented a case of severe hemorrhagic cystitis remitted successfully by the treatment for underlying aplastic anemia.

Introduction

Hemorrhagic cystitis (HC) is a rare disease that can occur following radiotherapy and chemotherapy, including cyclophosphamide regimens. HC is characterized by diffuse bleeding from the bladder mucosa. By contrast with infectious cystitis, HC is a potentially deadly complication (1). Treatment for this difficult disease requires a wide range of invasiveness. For example, intravenous, endoscopic and instillation therapy (aluminium hydroxide, magnesium hydroxide aminocaproic acid, alum, silver nitrate solution) (2-5), hyperbaric oxygen therapy and a vascular approach (selective embolization of the internal iliac arteries) may be possible conservative therapies (6,7). Total cystectomy may be a final option for patients with refractory HC (8). However, high risk of perioperative complications and mortality associated with surgery should be taken into consideration. Aplastic anemia (AA) is a rare blood disorder and patients commonly present with pancytopenia, increasing the risk of bleeding complications, which can be fatal if left untreated (9). The present study reported severe HC, which was unable to be managed with several conservative therapies, however, improved by treatment for underlying AA that was diagnosed belatedly.

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Case report

A 70-year-old male was diagnosed to exhibit prostate cancer with cT3aN0M0, initial prostate specific antigen 19.3 ng/ml, and a Gleason score 5+4. The patient was treated by high dose rate brachytherapy (19 Gy), followed by external beam radiotherapy (EBRT; 46 Gy) for the whole pelvis, with combined androgen blockade (leuprolide acetate and bicalutamide). Following 3 years of radiotherapy, urinary retention and macroscopic hematuria occurred. Ultrasonography revealed bladder tamponade and left hydronephrosis. Abdominal computed tomography and magnetic resonance imaging revealed no specific findings of the cause. As many minor bleedings were observed in the bladder mucosa by cystoscopy, trans-urethral coagulation was performed (Fig. 1). The posterior wall and the urethral triangle in the bladder were edematous, however, neither major bleeding or a cancerous lesion were detected at this time. A long hematoma from the left ureteral orifice was identified and retrograde pyelography revealed a distorted lesion of the left lower ureter. However, urine cytology from the left ureter revealed no malignancy. Biopsy of the bladder mucosa and ureteroscopy to the left ureter revealed no evidence of disease. Finally, radiation-induced HC was clinically diagnosed with no clear evidence of other diseases. As the hematuria was very severe and associated with frequent bladder tamponade and deteriorating anemia, trans-urethral coagulations were performed repeatedly during the next few months. Intravesical instillation of the mixed compound of aluminium hydroxide and magnesium hydroxide was administered, followed by hyperbaric oxygen therapy. Nevertheless, no improvement of clinical symptom was observed. Subsequent bilateral hydronephroses and renal impairment with the serum creatinine level of 8.72 mg/dl was developed and required the

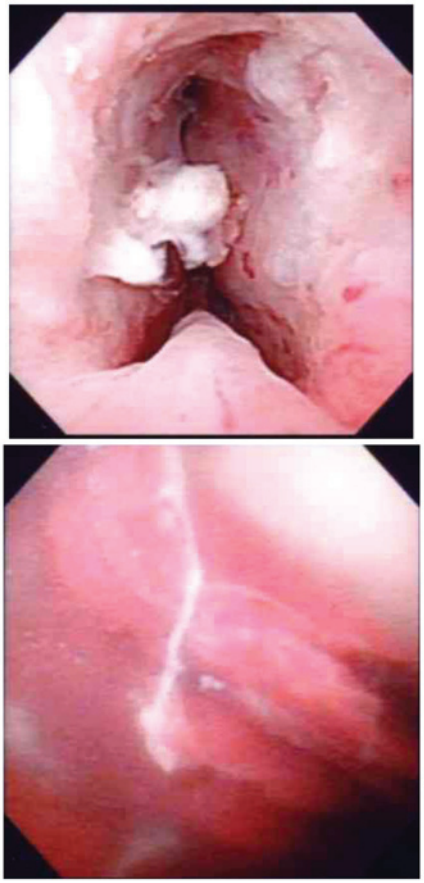

Figure 1. Cystoscopy revealed fur deposition and rough mucosa on the prostatic urethra (upper) and mucosal edema with coagula in the bladder (lower).

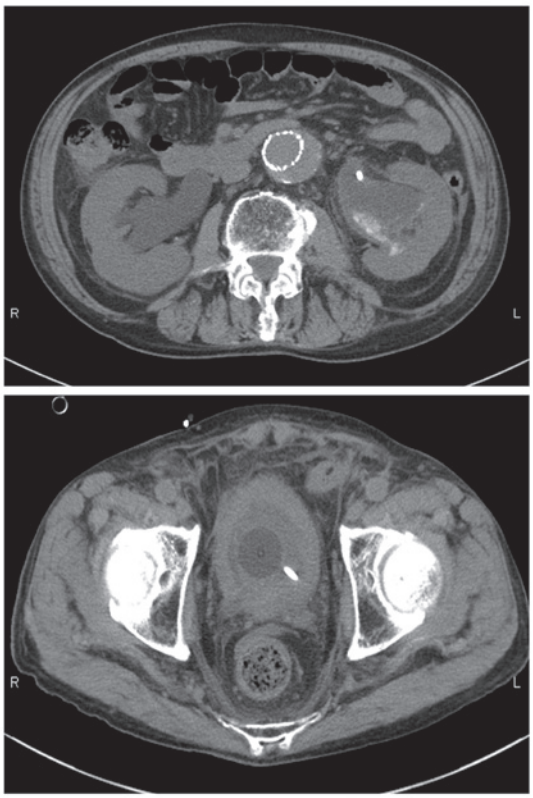

Figure 2. Abdominal computed tomography scan prior to bilateral percutaneous nephrostomies revealed bilateral hydronephroses (upper) and bladder wall thickness with coagula tamponade (lower).

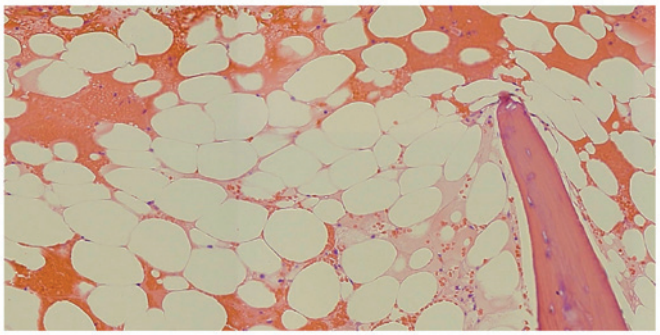

Figure 3. Microscopic appearance of a bone marrow filled with adipose tissue is consistent with aplastic anemia.

induction of hemodialysis as well as bilateral percutaneous nephrostomy (Fig. 2). A blood test revealed pancytopenia and transfusions of red blood cells and platelets were required every other day. When total cystectomy with urinary diversion was considered for this difficult condition, aplastic anemia (AA) was diagnosed by the bone marrow examination (Fig. 3). Administration of cyclosporine and anabolic steroid was initiated by hematologists, and macroscopic hematuria was gradually improved. Subsequently, renal impairment markedly improved to <1.0 mg/dl in the serum creatinine level. The incidence of transfusions of red blood cells and platelets was decreased to once a week thereafter.

Discussion

HC is defined as a diffuse inflammatory change of the bladder characterized by sustained hematuria or lower urinary tract symptom (10). HC may occur following bone marrow transplantation, peripheral blood stem cell transplantation, radiotherapy to the pelvic organ, chemotherapy using cyclophosphamide, and specific viral infections (10). It is hypothesized that as a result of mucosal edema and inflammation by radiotherapy, telangiectasia and interstitial fibrosis occur, resulting in decreased bladder capacity and compliance (11). Finally, mucosal ischemia, ulceration and bleeding occur. HC can occur generally between 6 months and 10 years after radiotherapy, affecting ~6.5% of patients following pelvic radiation (11). Leapman *et al* (12) reported cystoscopy findings of 2,532 males treated with prostate brachytherapy with or without EBRT. Of those, 13 individuals, (0.51%) were diagnosed with radiation cystitis, and 8 received combined brachytherapy with EBRT, although the total biological effective dose was similar among these groups (208.6, compared with 200 Gy; P=0.092). Lawton *et al* (13) reported that the risk of HC increases with higher doses of radiation (>70 Gy) and a larger treatment area (13). On the other hand, Fuentes-Raspall *et al* (14) analyzed 257 patients treated with EBRT for prostate cancer. They reported that late rectal toxicity was associated with the volume irradiated, however, could not correlate with the bladder volume (14). Further studies are required to investigate whether irradiated volume is a risk factor for HC. Treatment of HC can range from simple bladder irrigation to invasive surgery. For refractory cases to conservative therapy, urinary diversion can be

considered. However, cystectomy for radiation cystitis is often more difficult. It was reported that the 90-day mortality rate in patients with HC undergoing a cystectomy was 16% (15). Cystectomy with urinary diversion is associated with a high rate of perioperative complications and radiation-induced fistula (14). The present study considered this challenging method, however, AA was accidentally diagnosed in the background of HC. On multivariate analysis, increased risk factors of HC were significantly associated with previous pelvic radiation (10). Although it is unclear whether AA is a risk factor for HC or not, treatment for AA improved symptoms caused by HC, perhaps as a result of hematopoietic improvement. Close examination in the background of HC is required in severe and treatment-resistant HC.

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