Successful embolization of internal iliac artery in a case of carcinoma cervix with haemorrhagic radiation cystitis

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Case Report

Abstract

Massive and intractable bladder hemorrhage can be potentially life-threatening and its management is a complex clinical problem for the Urologists and Oncologists; causing significant morbidity to the patients and escalating the cost of management. Advanced pelvic urological malignancy, radiation cystitis, cyclophosphamide-induced cystitis and severe infection are the most common causes of intractable haematuria. Management options include bladder irrigation and supportive transfusion, intravesical instillation, endourological intervention, and surgical intervention by means of ligation of internal iliac arteries or salvage cystectomy which has poor success and high morbidity rates. Trans-arterial embolization offers another minimally invasive, safe and effective option. We report a patient with severe hemorrhagic cystitis who failed to respond to conventional supportive measures including alum irrigation and was successfully managed with super selective embolization of left superior vesical artery.

Keywords: Cystitis; Embolization; Therapeutic; Hemorrhage; Radiation; Carcinoma Cervix

Introduction

Hemorrhagic cystitis is defined as a diffuse inflammatory condition of the urinary bladder due to an infectious or noninfectious etiology resulting in bleeding from the bladder mucosa.1 Chronic recurrent hemorrhagic cystitis can cause intractable haematuria and has several causes, including pelvic radiation and systemic treatment with oxazophosphorine alkylating agents like cyclophosphamide.2 Intractable haematuria from the bladder can be life threatening and its management is challenging and frustrating for the treating Urologist and Oncologist.1,2 The incidence of radiation cystitis in general is between 3-15%.2

Infectious etiologies are less common causes of chronic hemorrhagic cystitis except in immunocompromised hosts like bone marrow transplant patients.3 Incidence of hemorrhagic cystitis (HC) in hemopoietic stem cell transplantation (HSCT) recipients is reported to be 7-52%, usually either related to the use of cyclophosphamide or to a viral infection.3

Conservative treatment of HC is based on irrigation of the bladder through a three-way catheter, or cystoscopic clot evacuation with cystodiathermy. Alternatively, if there is recurrence or the treatment fails, irrigation with silver nitrate or alum solution, instillation of formalin and Helmstein balloon compression have been described.4 In the past the failure of conservative treatment could even necessitate open surgical bilateral ligation of the internal iliac arteries as a final option. However, such a procedure in a terminally ill patient would carry an unacceptable morbidity. There has been a continuing search for a minimally invasive, less morbid procedure to offer to these patients before they have exsanguinated.5

In these situations, selective trans-arterial embolization (TAE) of the internal iliac arteries can be a reasonable and effective treatment option.4

Here, we present a case of radiation-induced hemorrhagic cystitis that was successfully treated with embolization of internal iliac artery. This case is being reported to increase awareness among treating clinicians regarding the safe and effective option of embolization of internal iliac artery for the treatment of intractable haematuria; and to give the readers an overview on management of such difficult cases. A brief review of current literature is also presented.

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Case presentation

A 63-year-old lady presented to Oncology department of a tertiary care hospital with the chief complaint of progressive, intermittent hematuria of 6 months duration. The patient was earlier treated 4 years ago as a case of Carcinoma Cervix FIGO IIA. She had received external beam radiotherapy to pelvis to a dose of 5000 cGy in 25 fractions over 5 weeks, concurrently with Inj Cisplatin 50 mg weekly infusion; followed by 3 fractions of intracavitary high dose rate brachytherapy of 7 Gy each. She attained complete response after chemo-radiation and was on periodic follow up. She was asymptomatic and disease free on all reviews until she developed haematuria 6 months ago for which she was managed conservatively in a local non-oncology centre. She continued to be symptomatic with hematuria and then reported to Oncology OPD. On examination, she had mild pallor though she was hemodynamically stable.

The patient underwent detailed workup for intractable hematuria. Her hemoglobin was 8 gm% and she was transfused 3 units of packed cells, rest of the hematological and biochemical profile was within normal limits. Her USG abdomen and pelvis was suggestive of presence of blood clots in urinary bladder with normal kidneys and pelvicalyceal system. CPE revealed multiple blood clots. Whole body PET CT showed eccentric wall thickening in urinary bladder (SUV-20.3).

Patient initially underwent clot evaluation under GA and was then kept on bladder irrigation with saline. Despite continuous bladder irrigation with normal saline she continued to have hematuria. She was then started on alum irrigation delivered as a 1% solution (50 g alum in 5 liter sterile water) at a rate of 250 ml/h for 4 days. However, she failed to respond to conservative measures and had persistent intractable hematuria along with pain lower abdomen, clot retention and bladder spasms. She was then referred to interventional radiologist for consideration of internal iliac artery embolization, which was attempted via right femoral access under local anesthesia. Bilateral selective internal iliac angiogram was done using 5F Cobra catheter. Internal iliac angiogram revealed bladder wall thickening with hypervascularity and blush predominantly from a hypertrophied superior and inferior vesical artery on left Figure 1(a). Super-selective catherization of superior vesical branch of anterior division of left internal iliac artery was done coaxially using 3.0 Fr Microferret infusion catheter (Cook Medical Inc, Bloomington USA) and embolized with 100-300 Embospheres, Merit Medical Systems, till technical end point of stasis and absence of hypervascularity in the superior vesical artery. This was followed by embolization of the left inferior vesical artery using a similar microcatheter and embolizing agent combination. Post-embolization DSA of the anterior division of internal iliac artery showed stasis in the embolized vessels and regression of the hypervascularity Figure 1(b). Selective right internal iliac artery angiography did not show any significant hypervascularity hence, embolization of right internal iliac was not done. She tolerated the procedure well, required post-procedure analgesic only on the day of the procedure and showed good symptomatic relief in hematuria. The patient is asymptomatic without recurrence of hematuria at periodic follow ups.

Discussion

Complications of pelvic radiation include both acute and chronic bladder injuries. One sequel of chronic radiation-induced bladder insults is hemorrhagic cystitis. The incidence of hemorrhagic cystitis for cervical carcinoma treated with both intracavitary and external beam radiotherapy is reported at 6.5%. The median interval to develop haematuria following the completion of therapy is about 35 months. Chronic
radiation therapy can cause damage to the bladder submucosa, leading to necrosis of the vascular endothelium, vessel wall thickening and oblitative endarteritis. All of these changes result in hypoxia, hypovascularity and ischaemia, which can ultimately induce neovascularization of vessels that are fragile and prone to bleeding.\textsuperscript{2,5,6}

Manifestations of radiation cystitis can range from minor, temporary, irritating voiding symptoms and painless, microscopic hematuria to more severe complications such as gross hematuria, contracted nonfunctional bladder, persistent incontinence, fistula formation, necrosis and death. The severity of hemorrhagic cystitis is graded as follows: 0 – No symptoms of bladder irritability or hemorrhage; 1 – Microscopic hematuria; 2 – Macroscopic hematuria; 3 – Macroscopic hematuria with small clots; and 4 – Massive macroscopic hematuria requiring instrumentation for clot evacuation and/or causing urinary obstruction.\textsuperscript{1,6} In all patients of hemorrhagic cystitis a thorough evaluation should be done to determine the cause; including urine cytology, upper tract imaging and cystoscopy, which often reveals neovascularity and telangiectasia characteristic of radiation cystitis. The patient’s current medications must be reviewed and anticoagulants must be stopped. Laboratory evaluation includes hemoglobin, complete blood count, blood urea, serum creatinine, and coagulation profile and urine culture. Patient should be hemodynamically stabilized with intravenous fluids and blood transfusion. Antibiotics are given until sterile cultures are obtained.\textsuperscript{1,4,6}

There are many treatment options for hemorrhagic cystitis. As a first step a large bore three-way Foley urethral catheter is inserted to decompress the bladder and start saline irrigation. In some instance cystoscopic clot evacuation may be necessary. During cystoscopy, bladder should be carefully evaluated for the source of bleeding and biopsy of suspicious malignant lesions or fulguration of bleeding spots can be done at the same time.\textsuperscript{1,4} Patients not responding to clot evacuation, and those with diffuse bleeding, require supplemental therapeutic techniques with systemic or intravesical agents namely oral aminocaproic acid, oestrogens, endoscopic laser coagulation, intramural orgotein, formalin, placental extract or prostaglandin administration, Helmstein’s hydrostatic distension, hyperbaric oxygen, sodium pentosan polysulphate, silver nitrate, vasopressin, phenol, urinary diversion and cystectomy.\textsuperscript{1,2}

Alum irrigation has traditionally been considered useful to treat hemorrhagic cystitis, with success rates reported as high as 75–100%. As an astringent, it causes protein precipitation, vasoconstriction and decreased capillary permeability without damaging normal urothelium. It is commonly delivered as a 1% solution (50 grams alum in 5 liter sterile water) via continuous bladder irrigation at a rate of 250 ml/h and shows its effect in 3–4 days.\textsuperscript{1,2} However, our patient failed to respond to alum irrigation and deteriorated symptomatically in the form of pain abdomen, bladder spasm, clot retraction and persistent hematuria. Moreover, aluminum toxicity due to its absorption has been reported such as microcystic hypochromic anemia, osteomalacia, dementia, encephalopathy, metabolic acidosis and coagulopathy, particularly in renal failure patients and in children.\textsuperscript{1,2} Hyperbaric oxygen therapy for HC patients has achieved encouraging success with no adverse effects in recent years, especially for HC induced from radiation, which allows better tissue diffusion of oxygen, improving neoangiogenesis by increasing the vascular density of irradiated tissues. However, the wide application of this approach is limited by the requirement of a hyperbaric chamber and long procedure spanning over 20–30 days.\textsuperscript{6}

Surgery is the last resort in patients of intractable massive hematuria. Various surgical procedures like urinary diversion including nephrostomy tube placement with occlusion of the ureteral orifices (balloons or glutaraldehyde cross-linked collagen), cystostomy with ureteral catheters, ileal loop diversion, ureterosigmoidostomy and cutaneous ureterostomy, open packing of the bladder, ligation of hypogastric arteries and cystectomy and urinary diversion have been described. The goal of supravesical diversion is to decrease exposure of the hemorrhagic areas to urokinase to allow for hemostasis.\textsuperscript{1,6} However, surgery is associated with significant morbidity and mortality in these cases as they are already immunocompromised in the backdrop of previous malignancy managed by pelvic radiotherapy with or without chemotherapy.\textsuperscript{1}

Selective and super selective embolization has been described as an effective and safe treatment option as an alternative to invasive surgical procedures for intractable HC secondary to radiation, tumors and trauma which is refractory to conventional treatments.\textsuperscript{6–10} Complications arising from the procedure are uncommon, and include sepsis, gluteal pain, gait disturbances and, very rarely, bladder necrosis. Compared with selective embolization and other methods, the advantages of super-selective embolization are a lower recurrence rate of bleeding and fewer side-effects, e.g. post-embolization gluteal pain, claudication or tissue necrosis, necessitating frequent morphine use. Embolization should be done with unresorbable particles and should be as distal as possible into the anterior division of the internal iliac artery, to preserve the gluteal artery and avoid complications such as severe pain in the buttocks and the upper thighs.\textsuperscript{4}

Various authors have evaluated the efficacy and long-term complications of transcatheter internal iliac
artery embolization as a palliative measure in the control of intractable hemorrhage from advanced pelvic malignancies invading bladder or as chemoradiation induced cystitis after conservative management had failed. Ligouri et al. evaluated the feasibility and efficacy of TAE in 44 patients with intractable HC secondary to advanced pelvic tumour arising from or invading the bladder. TAE of the internal iliac arteries produced initial complete control of bleeding in 36 of the 44 patients (82%). At a mean follow-up of 10.5 months post TAE there was permanent control of bleeding in 19 (43%) patients while a second TAE session was used in five (11%) patients. During the follow-up there were no major complications related to TAE. Han and colleagues investigated the role of selective embolization of the internal iliac arteries in patients with severe HC after HSCT. A retrograde arterial catheterization of the femoral artery by modified Seldinger's technique was used to perform digital angiography of the aortoiliac sector. Selective embolization of the internal iliac arteries was then performed with gelatin sponge to confirm the occlusion of the vesical hypervascularization. Eight out of ten patients achieved complete response (CR) without any major complication, their hematuria and symptoms ceased after embolization treatment, including six from first treatment of embolization and two from second treatment.

Nabi and colleagues managed six patients with advanced pelvic malignancies and intractable hematuria with embolization using permanent coils in the anterior division of internal iliac artery bilaterally. All patients except one were successfully embolized in a single setting with no complications. Bleeding was successfully controlled in one patient at the second attempt of embolization. At a mean follow-up of 22 months, no patient had a recurrence of bleeding. Payne et al. studied 10 patients with severe HC who underwent selective embolization using gelatin sponge particles or pledgets, after all the conservative measures for controlling hematuria had failed. Eight of 10 patients (80%) achieved CR, including six from first treatment of embolization, two from second treatment, no further therapy was required in all the patients after CR. In another study by El-Assmy seven patients underwent TAE of anterior division of internal iliac artery bilaterally for intractable bladder hemorrhage. TAE was successful in immediate control of severe hemorrhage in all seven patients after a mean period of 4 days. In a study by Delgal et al. 18 out of 20 patients who had failed to respond to conservative treatment for HC could be successfully embolised, including bilateral and unilateral embolization in 13 and 5 respectively.

**Conclusion**

To conclude, internal iliac artery embolization is a feasible, effective and minimally invasive option while managing late onset hemorrhagic cystitis in carcinoma cervix patients in post pelvic radiotherapy scenario; and also in advanced pelvic urological malignancies presenting with intractable bleeding.

**Conflict of interest**

The authors declare that they have no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

**References**