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Alum instillation: A management option for intractable hemorrhagic cystitis

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Abstract:

Intractable hemorrhagic cystitis is an uncommon but significant treatment complication of concurrent chemoradiation therapy for cervical cancer. Alum instillation is regarded as a safe and effective option for its treatment. This case presentation will discuss a patient who presented with postradiation cystitis and was treated with alum irrigation. The aim of this report is to offer alum irrigation as a management option for intractable hematuria.

Keywords:

Alum irrigation, cancer survivorship, intractable hematuria, postradiation cystitis

Introduction

Cervical cancer continues to be the second most frequent cancer in the country. Improvements in diagnosis and treatment of cervical cancer, preventive strategies, and building public awareness have positively affected the burden of this disease to our community. However, often overlooked opportunities for improvement are the medical and social issues related to cancer survivorship. Hemorrhagic cystitis (HC) is reported as a late complication of chemoradiation in 6.6%–9% of patients which can lead to uncontrolled hematuria and death in 75%.[1]

The index patient completed treatment for cervical cancer with concurrent chemoradiation and had no evidence of disease for 7 years. However, a treatment complication of postradiation cystitis plagued her necessitating frequent hospitalization and blood transfusion, which placed a huge strain in her ability to become a wage earner for her family, in addition to the hospital expenses adding to her financial distress.

This report will discuss a case of intractable HC treated with alum irrigation. This report aims to increase awareness regarding alum irrigation as a safe and readily available option for the treatment of intractable hematuria cystitis (IHC).

Case Report

The index patient has been previously diagnosed with Stage IIIB squamous cell carcinoma, large cell, nonkeratinizing subtype and completed the treatment plan of concurrent chemotherapy and radiation therapy (CCRT). Her postradiation course was unremarkable until she presented with hematuria, 6 years after chemoradiation. In addition, she reported a sensation of incomplete bladder emptying and voiding difficulty to her oncologist. She was referred to the urogynecology service and underwent diagnostic cystourethroscopy with biopsy which revealed urothelial epithelium with chronic inflammation and urothelial papilloma. She was managed as a case of voiding dysfunction probably secondary to radiation cystitis. Her symptoms were relieved with bladder training, clean intermittent self-catheterization, and topical estrogen.

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Five months after the initial management, she was seen in the emergency department due to severe suprapubic pain and urinary retention. The urinary retention was the result of a bladder outlet obstruction caused by the blood clots from postradiation HC. After cystoclysis, she underwent cystourethroscopy which demonstrated mucosal edema, hyperemia and hypervascularity of the entire bladder. There were blood clots and desquamated tissue within the vesical cavity [Figure 1]. No tumors or calculi were seen.

During her 3rd admission 1 month later [Figure 2], irrigation with one liter of one percent Alum solution was performed at a rate of 80 gtts per minute for 2 cycles with note of cessation of gross hematuria and improvement of flow. She was monitored in the ward and monitored for adverse events [Table 1]. She complained of severe bladder spasms which were addressed with a decrease in alum irrigation flow rate to 60 gtts/min, anticholinergic therapy, and pain management. Alum instillation was alternated with cystoclysis to clear blood clot formation. She was discharged with a resolution of gross hematuria and blood clot formation.

She was admitted for the 4th time, to complete a total of four cycles of alum irrigation. Before this admission, she reported blood-tinged urine and occasional blood clots. One liter of 1% alum solution was performed at a rate of 80 gtts/min for 2 cycles continuously. Gross hematuria completely stopped, and no further hospital admissions were made for blood transfusion.

However, patient had difficulty voiding spontaneously and needed frequent transurethral catheterization. Unfortunately, despite estrogen application and urethral dilatation, urethral stricture persisted and the suprapubic catheter was maintained. In addition, vaginal stenosis also persisted despite vaginal dilatation [Figure 3].

In the interim, the patient was able to do duties limited to domestic chores and activities of daily living. Despite a suprapubic catheter in tow, she was able to attend social functions and eventually went for regular clinic follow-ups by herself.

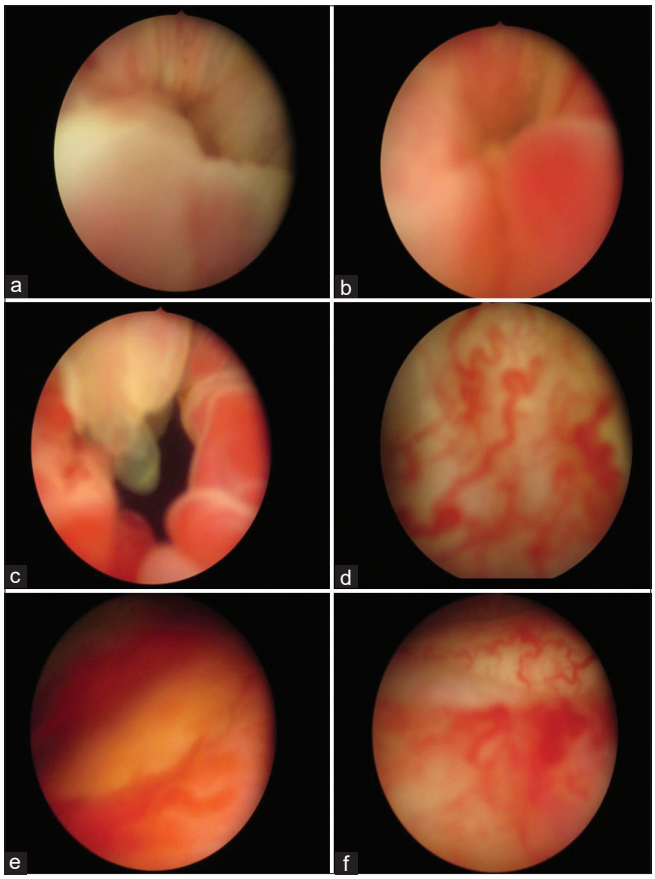

Figure 1: Diagnostic Urethroscopy and cystoscopy during first admission. Intraoperative findings: (a) On urethroscopy, the urethral mucosa was pale and smooth, (b) The urethrovesical junction was intact, (c) There were papillary fronds over the urethrovesical junction, On cystoscopy, the trigone (not shown) was hyperemic and fibrotic. Bilateral ureteral orifices were patent with good efflux of urine (not shown), (d-f) The right, left, posterior bladder wall and dome were edematous, hyperemic, and hypervascular. There were blood clots and desquamated tissue within the vesical cavity

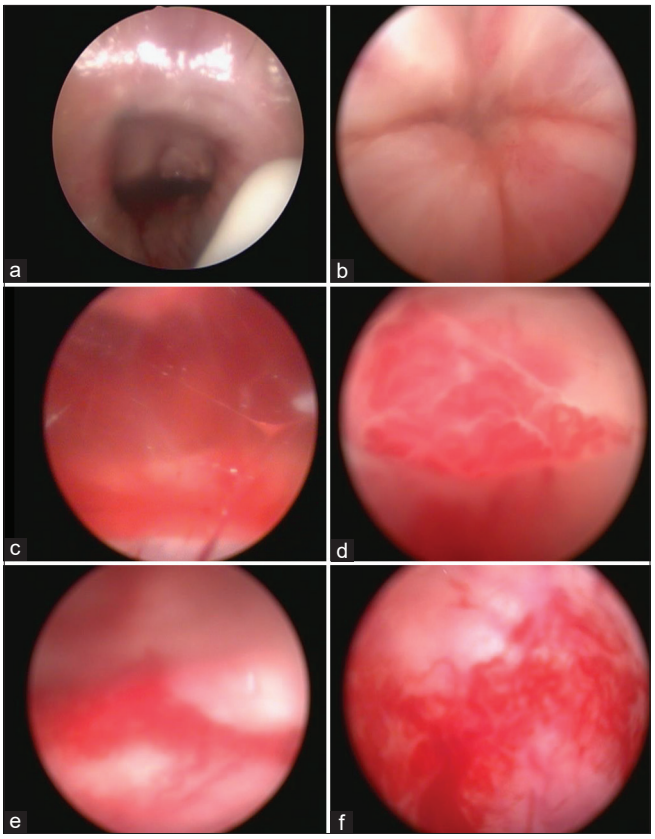

Figure 2: Diagnostic Cystourethroscopy during third admission. (a) The urethral mucosa was smooth and very pale, (b) The urethrovesical junction was intact, (c and d) The trigone was smooth and pale with numerous tortuous bed of blood vessels. Bilateral ureteral orifices were difficult to visualize (not shown), (e and f) There was a bed of bleeding vessels at the left posterior bladder

Figure 3: Urethral stricture

At 20 months after alum instillation, the patient reported blood-stained urine per suprapubic catheter once to twice a month associated with strenuous activities. At 22 months, the patient consulted in the emergency room department due to acute urinary retention which probably resulted from bladder outlet obstruction secondary to blood clots which was resolved by flushing the catheter with normal saline solution. No recurrence of gross hematuria of urinary retention followed thereafter.

During the course of this long-term follow-up with the patient, the frequent visits in the hospital made it difficult to get and keep a job. However, the patient remains content to be independent and relatively symptom free.

Discussion

Current estimates indicate that 7190 Filipino women are diagnosed with cervical cancer annually and 4088 die from the disease.[2] Because of established screening programs, younger women are diagnosed and treated earlier. These women, younger and premenopausal survivors, are challenged by the aftermath of their treatments. Quality of life issues arise as a result of treatment-induced ovarian dysfunction and its corresponding vasomotor functions. Disruptions in their family structures with regard to marital relationships, concerns for the care of young children, employment bias, and economic issues all add to the burden of younger survivors.

Pelvic RT for pelvic malignancies can lead to long-term collateral damage to the bladder. Late sequelae may present many years after treatment. This includes incontinence, pain, and hematuria. In the Philippines, local data on HC are few and probably underreported. Symptoms may be insidious and start as an inconvenient incontinence but may lead to gross hematuria that, in rare occasions, may become fatal. Therefore, knowledge on management and treatment options of HC is vital.

RT directly delivers high-energy particles to the tumor, albeit some collateral damage to the neighboring tissues is inevitable despite precautionary measures and treatment advancements. The incidence and severity of RT side effects depend on the site, volume of tissue exposed, schedule and total dose, dose per fraction, and radiation type. Although HC has been reported to occur in up to 9% of patients who have received full-dose RT, it may be a severe and potentially life-threatening complication in 75%. The onset is typically 1–3 years after treatment; however, patients with a history of pelvic radiation can develop rectal cancer many years after RT.[1,3]

High-energy radiation can cause cell death through DNA damage or an increase in the permeability of cell membranes. The bladder urothelium has a low cell turnover rate, so it becomes susceptible to radiation damage, with urine acting as a strong irritant adding to the inflammation of the bladder wall. Late tissue injuries include obliterating endarteritis, fibrosis, telangiectasia, and hematuria. Tissue ischemia can also lead to ulcer and fistula formation.[3]

Table 1: Laboratories done during alum instillation

Date	Urine CS CFU/ml	Na 137-145 mmol/L	K 3.5-5.1 mmol/L	Cl 98-107 mmol/L	BUN 7-17 mmol/L	Crea 46-92 umol/L	Hgb 120-160	Hct 0.38-0.47	WBC 4.5-11	Platelet 150-450	PT	aPTT
Third admission 11/07/2018	50,000 Enterococcus faecalis	139	3.4	108	1.6	0.81	70	0.27	7	256		
11/21/2018	E. coli 50,000 CFU/ml	142	4.4	111	2.5	75	128	0.29	6.9	388	12.9/14.5 80% INR 1.16	30.38s/ 27.2s
Fourth admission 12/11/2018	Klebsiella pneumonia 100,00 CFU/ml	141	3.8	108	4.3	86	64	0.26	4.8	322	12.9/12.9/100% INR 1.0	30.38s/ 26.8s
12/16/2018	Enterococcus faecalis 50,000					76	102	0.31	5.4	263		

E. faecalis: Enterococcus faecalis, K. pneumoniae: Klebsiella pneumoniae, E. coli: Escherichia coli, BUN: Blood urea nitrogen, WBC: White blood cell, aPTT: Activated partial thromboplastin time, PT: Prothrombin time, Hgb: Hemoglobin, Urine CS: Urine culture studies

The index patient presented with postradiation HC, 7 years after completing chemoradiation for cervical cancer.

Despite standard treatment strategies, she had repeated episodes of gross hematuria, blood clot formation, and developed urethral stricture, necessitating suprapubic catheterization. Intravesical instillation therapy with alum potassium sulfate was instituted.

Intravesical alum is purported to serve as an astringent that causes protein precipitation in the interstitial spaces and cell membrane. This mechanism leads to extracellular matrix contraction, along with vasoconstriction and sclerosis of exposed capillary endothelium, and decreased capillary permeability.[3]

After the first described intravesical alum irrigation by Ostroff and Chenault in 1982, for the treatment of HC in six patients, several small case series followed with a reported success rate of 50%–100%, with patients avoiding repeat admissions for HC-related issues at a median of 17 months after receiving alum.[4] Overall, alum was well tolerated. Identified side effects included bladder spasms, urinary tract infections, asymptomatic elevation in blood aluminum levels, and other side effects attributed to anticholinergic use such as altered sensorium.

Locally, there is a scarcity of reports on hemorrhagic cystitis. Utilizing the HERDIN database, a local study involving 129 patients with gross hematuria in both male and female cohorts was identified. The study concluded by establishing a correlation between gross hematuria and potential bladder malignancy, although it did not delineate specific management strategies for hematuria.[5] There was also a report on formalin instillation for intractable HC but with vague description on their management technique.[6]

Alum powder is inexpensive, but the labor requirements for pharmacy are intense due to dissolution issues, which may cause delays in treatment. There are two protocols for 1% alum irrigation. The first is to dissolve 400 g of potash of alum in 4 L of hot, sterile water. Three hundred milliliters of this stock solution is added to 3 L of 0.9% saline through a sterilizing filter and the bladder is irrigated with up to 30 L of this solution in 24 h. The second method is to dissolve 50 g of alum in 5 L of sterile water and irrigate the bladder at 250–300 mL/h. Schootstra *et al*. used 0.5% alum by dissolving 300 g of alum (aluminum potassium sulfate) and 480 g of sodium chloride in 60 L of water, with the advantages of decreased aluminum toxicity and minimization of colloid-like precipitation that can block the catheter.[7] One percent alum irrigation was used in this case.[8]

Other intravesical options are prostaglandin, silver nitrate, and formalin. However, these agents are more associated with the formation of hard clots, extreme pain, and long-term damage. If instillation therapies fail, international literature suggests hyperbaric oxygen, embolization, and surgery.[9]

For this patient, the expected outcome with alum irrigation was cessation of hematuria and improvement of urine flow to preclude repeated hospitalizations. In a recent study of 39 patients who were symptomatic despite bladder irrigation and clot evacuation, alum use decreased the patient's blood transfusions (23/39). Twenty-four patients (60%) required no additional therapy before hospital discharge.[7] Following alum irrigation, the patient had good urine flow and no recurrence of symptoms for 19 months. She was able to take care of herself and her daughter and resume her normal activities to some extent. Twenty months after alum installation, the patient reported blood-tinged urine and poor output from her suprapubic catheter. The

option of urinary diversion was offered again, but she remains hesitant to undergo the procedure.

Internationally, reports such as that of Guven *et al*. provided treatment algorithms but none has been accepted as standard treatment guideline.[10] Because radiation cystitis may be underreported in our local setting, this makes the interpretation of known treatment regimens difficult. The authors propose using a grading system for hematuria events as described by the Radiation Therapy Oncology Group [Table 2] to define which patients are presenting with mild or severe cases. Devries and Freiha devised a more clinical grading system based on the intravascular effects of hematuria. Mild hemorrhage does not produce an acute decrease in hematocrit and can be controlled by simple measures. Moderate bladder hemorrhage produces a decrease in hematocrit over several days and requires 6 units or less of transfused packed red blood cells (RBCs) to maintain hemodynamic stability. They defined severe hemorrhage as hematuria that is refractory to basic irrigation methods, and with transfusion of more than 6 units of packed red blood cells.[11] This grading system may influence the aggressiveness of treatment as the dynamics of the given episode and grade of bleeding are laid out. Hence, early intervention can be done while the HC is in the mild-to-moderate range and more readily responsive. The management of this case report parallels the Australian Westmead Hospital approach for treatment of HC[12] [Figure 4]. Upon recognition of a causative source, optimization of coagulative parameters was corrected followed by continuous bladder irrigation. As the hematuria remained refractory to this treatment, intravesical alum irrigation was then initiated.

Table 2: Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer grading of hematuria events

Hematuria morbidity	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Acute hemorrhagic radiation cystitis (RTOG scale)	NA	NA	Gross hematuria with or without clot passage	Hematuria requiring transfusion	Death from uncontrolled hematuria
Late hemorrhagic radiation cystitis (RTOG/EORTC scale)	Minor telangiectasia (microscopic hematuria)	Generalized telangiectasia (macroscopic hematuria)	Severe generalized telangiectasia (macroscopic hematuria)	Severe hemorrhagic cystitis	Death from uncontrolled hematuria

EORTC. European Organization for Research and Treatment of Cancer; RTOG, Radiation Therapy Oncology Group; NA, not applicable

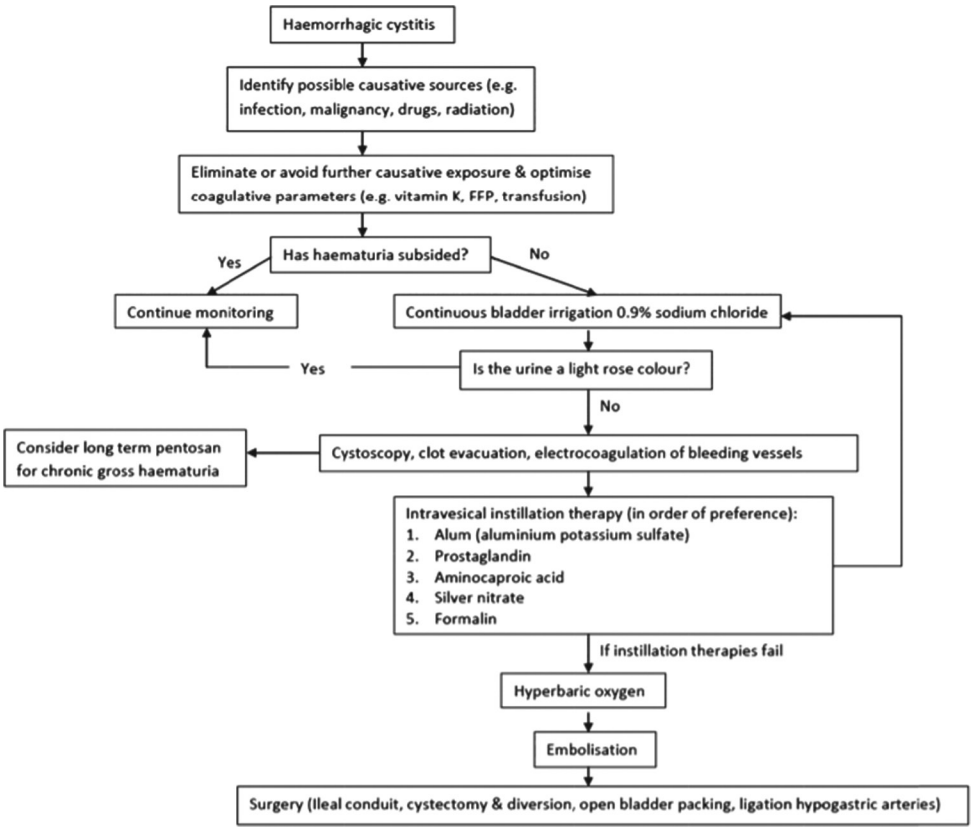

Figure 4: Westmead Hospital's approach for the treatment of hemorrhagic cystitis

Summary

It is recognized that alum irrigation is generally safe, effective, and at low cost compared to other treatment methods for IHC. It can be done at bedside without need for regional or general anesthesia. In previous case reports, intravesical alum irrigation does not cause local tissue distortion upon follow-up cystoscopy.[13]

Its clinical utility has been studied in case reports of IHC wherein the etiologies vary, such as radiation cystitis, chemotherapy-induced cystitis, or the rare infectious HC seen in the immunocompromised and organ-transplant recipients.[14] However, side effects include suprapubic pain and bladder spasms which can be addressed by analgesics and anticholinergic medications. There are also rare reports of serum aluminum levels and encephalopathy in patients with renal insufficiency. It is also acknowledged that although alum may be effective in decreasing the bleeding, it does not stop HC permanently. In addition, its success may be hindered by the common problem wherein alum forms a thick precipitate that clogs the catheters and coats the urothelium. This presents as a problem when alum irrigation fails, and it has been necessary but difficult to clear the bladder of the thick adherent precipitate before initiating further therapy. For this reason, standard treatment should be sought to treat IHC before resorting to alum or other methods that are more associated with the formation of hard clots, extreme pain, and long-term, irreversible damage. The challenge remains to improve reporting of postcancer treatment morbidities such as HC for vigilance in the effectivity and practicality of alum treatment in our local setting. The establishment of such treatment practices should definitely uplift the cancer survivorship of our patients, as the stigma of pelvic malignancies continues even after enduring the disease.

Informed consent

The patient has provided written informed consent for the publication of this case report, including the use of relevant images.

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Authorship contributions

Lilibeth M. Lim Navarro, MD - Concepts, Investigation, and Manuscript writing.

Joanne Karen S. Aguinaldo, MD - Concepts, Design, Definition of intellectual content, Manuscript writing.

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Conflicts of interest

There are no conflicts of interest.

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