



Case report

Cyclophosphamide-induced intractable hemorrhagic cystitis treated with hyperbaric oxygenation and intravesical sodium hyaluronate

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ABSTRACT

Cyclophosphamide is a well-known cause of hemorrhagic cystitis. However, the best treatment for hemorrhagic cystitis is still unknown. Herein, we present a patient with cyclophosphamide-induced hemorrhagic cystitis. The patient had a history of myasthenia gravis and had received cyclophosphamide therapy for 14 years. He was admitted due to gross hematuria, which was initially treated by cystoscopic fulguration, followed by continuous bladder irrigation. Due to refractory hemorrhaging, fulguration was repeated and percutaneous suprapubic cystostomy was performed. The bladder hemorrhage eventually subsided after hyperbaric oxygen therapy and intravesical sodium hyaluronate instillation. The combination of hyperbaric oxygen therapy and intravesical sodium hyaluronate instillation may be useful in severe hemorrhagic cystitis caused by cyclophosphamide.

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1. Introduction

Cyclophosphamide, an oxaphosphorine, is a well-known cause of hemorrhagic cystitis. A urinary metabolite of cyclophosphamide, acrolein, is believed to be responsible for hemorrhagic cystitis.¹ The best treatment for hemorrhagic cystitis is still unknown. Herein, we present a patient with cyclophosphamide-induced intractable hemorrhagic cystitis treated successfully after fulguration, hyperbaric oxygenation (HBO), and intravesical sodium hyaluronate.

2. Case report

A 62-year-old man had a history of thymoma with myasthenia gravis. He had received a thymectomy 16 years previously and had taken oral cyclophosphamide 25 mg daily for 14 years. Three years prior to this admission, urothelial carcinoma of the urinary bladder, with carcinoma *in situ*, was diagnosed at a local hospital.

The patient complained of intermittent gross hematuria for several years, which progressed for 1 month. He visited a local hospital, and abdominal computed tomography revealed diffuse

thickening of the bladder wall with blood clots inside. He subsequently received cystoscopic fulguration at the local hospital. However, repeated gross hematuria with blood clot-induced Foley catheter obstruction occurred. In this case, massive blood transfusion was also required due to anemia. He was then transferred to our hospital.

Cystoscopic fulguration (Fig. 1) and a random bladder wall biopsy were performed; the pathology report showed no malignancy. However, severe hematuria was still noted despite continuous bladder irrigation with normal saline and intravenous mesna. Due to the refractory bladder hemorrhage, fulguration was performed twice on the 6th hospital day and 21st hospital day, and suprapubic cystostomy was carried out to prevent bladder distension. The patient had four sessions of HBO, at 1.5 bar for 90 minutes, during the hospital stay. The bladder hemorrhage subsided, and he was discharged on the 27th hospital day. In total, 22 units of packed red blood cell were transfused. However, he still complained of intermittent gross hematuria, and 1 month after discharge, cystoscopy revealed sloughy bladder mucosa (Fig. 2). Another 10 sessions of HBO and six cycles of intravesical sodium hyaluronate, 40 mg/50 mL, at an interval of 1 week were given. The gross hematuria gradually subsided, although he still complained of voiding frequency (16–18 times in the day hours), urgency, and nocturia (4–5 times at night). Four months after discharge, cystoscopy revealed no more oozing from the bladder mucosa (Fig. 3). Erythematous mucosa was still seen over the right lateral wall of the bladder; however, he no longer

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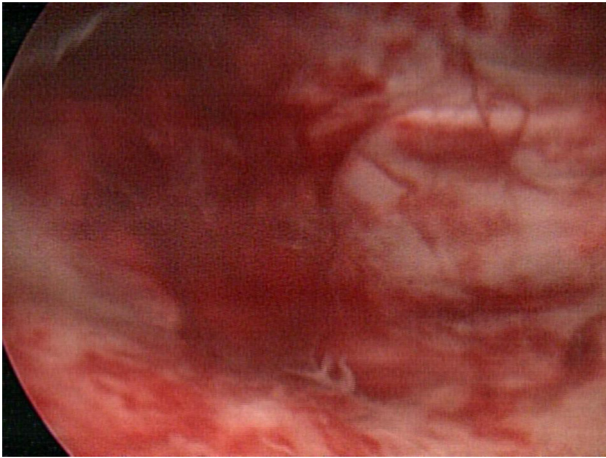


Fig. 1. Cystoscopic finding during the first fulguration revealed diffuse oozing of bladder mucosa.



Fig. 3. Four months after discharge, erythematous lesions mostly subsided. Scar formation was seen. There was no more oozing.

complained of gross hematuria. The dysuria, urgency, and urinary frequency also improved with antimuscarinic treatment.

3. Discussion

Cyclophosphamide is an immunosuppressive agent that is used for systemic lupus erythematosus, Wegener's granulomatosis, and rheumatoid arthritis. For myasthenia gravis, high-dose cyclophosphamide acts as an immunomodulator to "reboot" the immune system by eliminating the mature immune system.² The main toxic effects include myelosuppression, hemorrhagic cystitis, alopecia, and gonadal damage.³ Cyclophosphamide causes hemorrhagic cystitis by renal excretion of its hepatic metabolite, acrolein, which is urotoxic. The reported incidence of cyclophosphamide-induced hemorrhagic cystitis ranges from 2% to 40%, and the average oral dose of cyclophosphamide that causes hemorrhagic cystitis is reported to be 90 g, with an average drugs usage duration of 38 months.⁴ The symptoms include gross hematuria, frequency, dysuria, burning, urgency, incontinence, and nocturia, and they may persist and reoccur for several years after stopping treatment.⁵ The best treatment for cyclophosphamide-induced hemorrhagic cystitis is prevention. Mesna, which conjugates acrolein in urine, is an effective prophylaxis against cyclophosphamide cystitis.⁶ Once hemorrhagic cystitis develops, adequate hydration is usually

sufficient to prevent cystitis. Various treatments for hemorrhagic cystitis have been applied for cyclophosphamide-induced hemorrhagic cystitis (Table 1).⁷ It can be treated with continuous saline irrigation; acetylcysteine has been shown to bind acrolein and has been used as a bladder instillation.⁸ Efficacy of intravesical instillation, with various substances including E-aminocaproic acid, formalin, alum, phenol, silver nitrate, prostaglandin, fibrin glue, and sodium hyaluronate, in treating bladder hemorrhages have been reported. In Miodosky et al's⁹ study, 85% of the patients responded partially or completely to sodium hyaluronate treatment, by different mechanisms including inhibition of immune complexes, adherence to polymorphonuclear cells, inhibition of leukocyte migration, regulation of fibroblast and endothelial cell proliferation, and enhancement of connective tissue healing. HBO has been tried in radiation-induced hemorrhagic cystitis and applied to cyclophosphamide-induced hemorrhagic cystitis in a few cases.¹⁰ Embolization or open ligation of the hypogastric arteries is another available option. Surgery is the last resort in patients with intractable massive hematuria.

The present case received oral cyclophosphamide 25 mg daily for 14 years, equal to more than 120 g cumulative dose. This is much more than the reported average dose of cyclophosphamide that causes hemorrhagic cystitis. Moreover, he had been diagnosed with urothelial carcinoma of the urinary bladder 3 years prior to this presentation, which may also have been related to cyclophosphamide. During a nearly-1-month hospital stay, he received fulguration of the bladder mucosa three times and 14 sessions of HBO were given subsequently, and the hematuria gradually subsided. After discharge, he was treated with weekly intravesical sodium hyaluronate for six cycles, and the hemorrhagic cystitis had not relapsed after 18 months of follow-up.

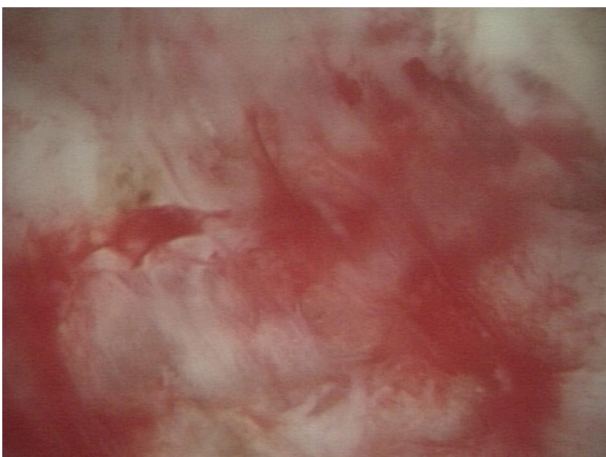


Fig. 2. One month after discharge, sloughy bladder mucosa was noted.

Table 1
Treatment of hemorrhagic cystitis.⁷

Continuous bladder irrigation	Cystoscopy and fulguration
Intravesical instillation	Oral agents
E-aminocaproic acid	Conjugated estrogens
Formalin	Sodium pentosan
Alum	Polysulfates
Phenol	Intravenous vasopressin
Silver nitrate	Hyperbaric oxygen therapy
Prostaglandin	Embolization
Fibrin glue	Cystectomy
Sodium hyaluronate	

Refractory cyclophosphamide-induced hemorrhagic cystitis can be life threatening. Various treatments have been reported; however, there is as yet no gold standard of therapy. A combination of different treatments that work by different mechanisms may increase the success rate. We suggest that combined cystoscopic fulguration (HBO and intravesical sodium hyaluronate) may be a useful treatment option for cyclophosphamide-induced hemorrhagic cystitis.

Conflicts of interest

The authors declare that they have no financial or non-financial conflicts of interest related to the subject matter or materials discussed in the manuscript.

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