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Review Article

Chronic Radiation cystitis: a review of medical and surgical management

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Abstract

Radiation cystitis is a complication of radiation treatment given for pelvic malignancies. Radiation cystitis can present as mild symptoms of dysuria, frequency, and hematuria to severe life-threatening complications like intractable hematuria, bladder perforation and contracted non-functional urinary bladder, fistula etc. Treatment is tailored according to the severity of symptoms and available treatment modalities sequentially. Initial treatment of hematuria is intravenous fluids, blood transfusions, cystoscopy and fulguration, irrigation with intravesical agents like alum, hyperbaric oxygen therapy, angioembolisation, urinary diversion and surgery (cystectomy). Radiation cystitis is associated with short- and long-term complications in pelvic malignancies patients. Early diagnosis, follow up, treatment is crucial for decreasing morbidity and mortality in these patients. In this review article we describe the current protocol in diagnosing and managing radiation cystitis.

Keywords *Pelvis, Radiation, Hematuria, intravesical treatments, Alum, formalin*

Introduction

Radiotherapy (RT) is the primary modality in the treatment of malignancies of the pelvis like carcinoma prostate, bladder, cervix, vulva, uterus, and ovaries. Although focused on organs of interest adjacent structures are still affected. It can cause radiation cystitis (Urinary bladder), urethritis (urethra), and proctitis (rectum) hampering the quality of life in these patients despite being cured of their primary disease. [1,2]

Radiation cystitis is inflammation and destruction of normal bladder urothelium and other layers after radiation exposure. [3]

Radiation exposure leads to normal urothelium damage by ionization or by free radical generation which further causes DNA damage by inhibiting protein synthesis and impairing replication. Radiation cystitis can occur acutely (Acute radiation cystitis) or after 6 to 24 months (Chronic radiation cystitis). Radiation dose, technique, fractionation, the total volume of tissue exposed, and duration of therapy determines the degree of damage to the urinary bladder. Although cystitis can develop at any dose, doses higher than 60 Gray is associated with more pronounced radiation cystitis. [4,5,6]

Symptoms of radiation cystitis range from frequency, urgency, dysuria, and pain to severe life-threatening hematuria to bladder perforation. These patients are investigated with blood investigations haemoglobin, RFT, LFT radiological investigations ultrasound, CECT, MRI, and cystoscopy. Treatment depends upon symptoms severity and complications.[1, 7, 8]

Radiation is useful for cancer treatment due to its ability to interfere with DNA synthesis and stop rapidly dividing cancer cells from completing mitosis. It also has this same effect on healthy, normally dividing cells surrounding the tumour. Another effect is decreasing blood supply to the irradiated area by causing oedema and fibrosis of the vessels (obliterative endarteritis) which can, in turn, lead to necrosis of tissue reliant on those vessels. [9]

Radiation cystitis is associated with short- and long-term complications in pelvic malignancies patients. Early diagnosis, follow up , treatment is crucial for decreasing morbidity and mortality in these patients. In this review article, we summarize the diagnosis and management of radiation cystitis.

Epidemiology

Radiation cystitis presents as moderate to severe hematuria in approximately 5% of patients after pelvic radiotherapy. It depends upon the radiation dose and method of delivery. It can occur after 6 months to 10 years after pelvic radiation.

Radiation cystitis is more common in males compared to females (2.8:1). Most patients present after a mean duration of 31.8 months after radiation exposure. [1,2]

Aetiology

Radiation causes the generation of free radicals and the ionisation of cells. It affects urothelium, blood vessels and detrusor. It leads to inflammation, oedema, and disruption of cellular junctions leading to sloughing and necrosis of urothelium. This causes penetration of urine into deeper bladder walls further aggravating inflammatory response. Normal blood vessels develop perivascular fibrosis, oedema, and necrosis. Radiation causes ischemia, chronic inflammation and oedema in the detrusor muscle. Chronic inflammation leads to neovascularization which causes the formation of friable vessels leading to frequent hematuria. [1,2,3]

Presentation

Acute radiation cystitis presents with lower urinary tract symptoms which can mimic urinary tract infections. Patients can present with frequency, urgency, hematuria, pain, Chronic cystitis develops after 3 months by inflammation, fibrosis, neovascularization, detrusor dysfunction, ischaemia, mucosal ulceration, hydronephrosis. [1]

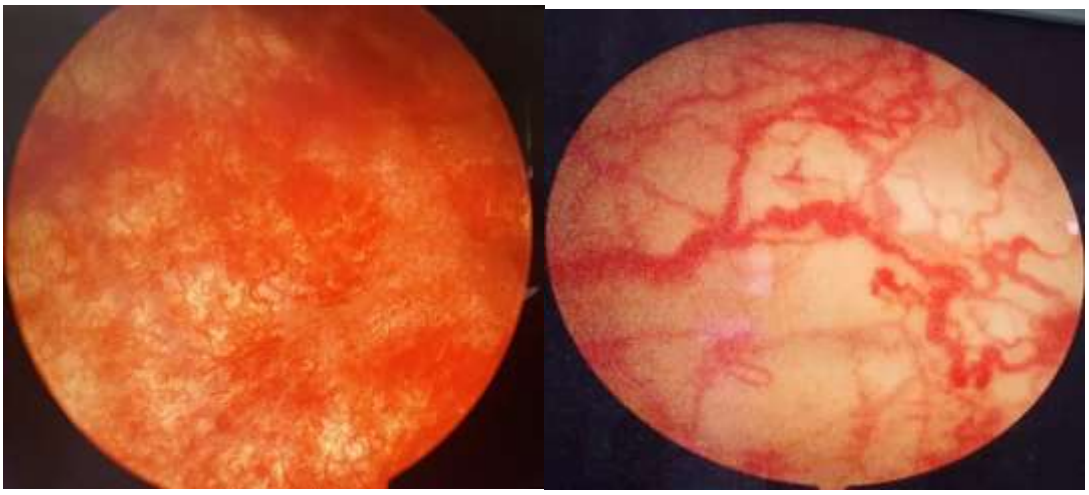

Figure 1: Cystoscopy showing cystitis (inflammation) and neovascularization

Figure 2: Clots evacuated from radiation cystitis patient

Diagnosis

Radiation Therapy Oncology Group (RTOG) divides symptoms according to severity into four grades.

Grade 1. Minimal epithelial injury, telangiectasia, microscopic hematuria

Grade 2. Moderate symptoms like frequency, urgency, macroscopic hematuria, urinary incontinence (intermittent), and generalized telangiectasia.

Grade 3. Severe symptoms frequency, urgency, hematuria, incontinence, decreased bladder capacity of less than 150 ml, severe telangiectasia.

Grade 4 Haemorrhagic cystitis, necrosis, fistula, bladder capacity less than 100ml other symptoms like perforation, incontinence requiring surgical treatment. [1]

Diagnosis is focusing on taking a complete history and detailed clinical examination. Urinalysis, cytology, and culture are done to diagnose infection and malignancies. Blood investigation of haemoglobin, RFT, LFT, and coagulation profile is done. Ultrasound is done to see the bladder wall and hydronephrosis. Cystoscopy should be done to grade the severity of radiation cystitis and be helpful to rule out primary or secondary bladder cancer. Cystoscopy shows bladder mucosa, bladder capacity, ureteric orifices, and severity of telangiectasia. [3]

Treatment / Management

Treatment of radiation cystitis depends according to severity of symptoms. Sequential management of hematuria is advocated as shown in the algorithm. Figure 3

For grade 1 and grade 2 Radiation cystitis, symptomatic relief with medication is typically all that is necessary. If frequency

and urgency are the predominant symptoms, anticholinergic medications can be used for relief. Pelvic pain and dysuria will require antibiotics, and analgesics if a urinary tract infection is diagnosed. Urinary bladder normal saline irrigation is considered the first-line treatment in all grades of hematuria secondary to radiation cystitis. [10]

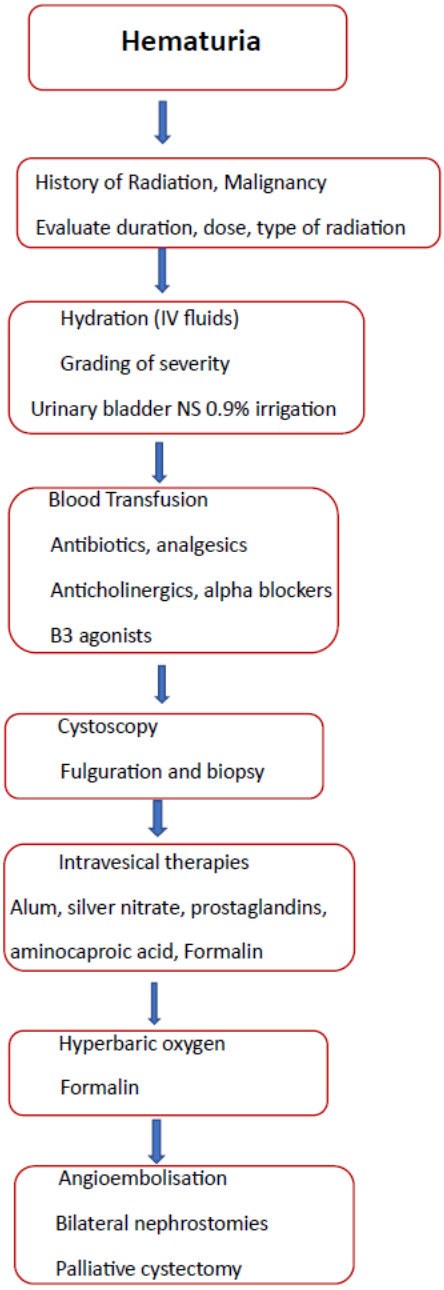

Figure 3: Algorithm to manage hematuria in radiation cystitis

Hematuria not controlled by urinary bladder irrigation will require cystoscopy and fulguration under general anaesthesia. The severity of radiation cystitis is graded; bleeding areas are fulgurated, and biopsy is taken from suspicious areas.

If hematuria is not controlled despite cystoscopy and fulguration will require Alum (Aluminium ammonium sulphate). Fifty grams of alum is dissolved in 5 litres of sterile water and urinary bladder irrigation is started at 250 t 300 ml/hr. It causes vasoconstriction, decreased permeability of capillaries, precipitation of proteins on urothelium along with astringent action. It can be instilled without anaesthesia and is the first intravesical therapy to be started after the failure of initial treatment. It can cause mild symptoms like suprapubic pain, and bladder spasms however in rare events systemic absorption can lead to aluminium toxicity. Aluminium toxicity can present as altered mental status which is more pronounced in renal failure patients. The success of alum instillation for control of hematuria ranges from 45- 100%.[2]

Payne et al described defects in glycosaminoglycans in urothelium as one of the causes of hematuria. Instillation of sodium hyaluronate intravesically was described. [11]

Silver nitrate 0.5 -1% is an intravesical instillation agent which can also be used effectively with minor adverse effects like suprapubic discomfort. It can be used repeatedly with short-lived effects in the control of hematuria due to radiation cystitis. [2,4]

Other intravesical agents like aminocaproic acid (lysine analogue competitive inhibitor of activators of plasminogen like urokinase), and prostaglandins are also described in control of hematuria refractory to treatment with varied degrees of success.[12]

Less commonly used options are Pentosan polysulfate sodium, intravesical ice water irrigations, oestrogens (orally or intravenous), intravesical hydrostatic pressure techniques, and argon beam coagulators. [4]

Hyperbaric Oxygen Therapy (HBOT) is another form of non-invasive treatment that has become more commonly used in recent years. HBOT increases vascularity by promoting angiogenesis hence maintaining normal function of urinary bladder. HBOT can achieve symptom relief and help in preventing progression of complications of radiation cystitis. It can achieves response rates ranging from 27% to 100% in radiation cystitis. [3, 13]

One study showed that, even with milder symptoms, patients treated within six months of hematuria onset had 96% complete or partial symptomatic resolution whereas those treated after six months had but a 66% response rate. This is supportive of (albeit not definitive for) the early use of hyperbaric oxygen therapy. [14]

If hematuria is not controlled despite all the above-mentioned modalities aggressive treatment is advocated. Intravesical formalin is successful in 80 to 90% of patients although it carries a high risk of toxicity. It is administrated under anaesthesia as a 1% solution which can be increased to 2% if needed. It acts by causing protein precipitation and occlusion of capillaries. Adverse effects of formalin instillation are decreased bladder capacity, fibrosis, ureteric stricture, and kidney injury. A cystogram before formalin instillation is advocated to rule out vesicoureteral reflux.

Selective Angioembolisation of the anterior branch of the internal iliac is advised in unstable patients which is successful in 80 to 90% of patients. It is a less invasive method of controlling intractable and recurrent hematuria before proceeding to cystectomy. [15]

Urinary diversion in the form of bilateral percutaneous nephrostomies is advised to divert urine. The aim of supra vesical diversion is to decrease urokinase exposure to unhealthy irradiated areas of the urinary bladder.

Surgeries in radiation cystitis carry significant morbidity and mortality. Cystectomy with diversion i.e., an ileal conduit is a treatment if all other modalities fail. In unstable patients, only diversion i.e., ileal conduit without cystectomy has been described. Difficult surgery is anticipated due to radiation-related fibrosis and inflammation although robotic surgery has been adopted for performing cystectomy in selected patients. [16]

Radiation cystitis symptomology varies greatly treatment should be tailored according to the severity and available

treatment. The treating physician should evaluate hematuria and should plan treatment after evaluating the risks and benefits of each treatment modality.

More invasive measures may be necessary if late-stage complications occur or if the radiation cystitis is resistant to more conservative methods. Such situations include persistent hematuria, fistulas, severe detrusor contraction, or hydronephrosis. Failure of more conservative measures leading to cystectomy is associated with a high risk of complications and mortality. Severe complications in almost half (42%) and 90-day mortality are reported to be 16%.

Prevention

Radiation cystitis carries high morbidity and mortality hence judicious use of radiation is advocated. Employing newer techniques for giving radiation (intensity and volumetric modulated radiotherapy) is a need of the hour.

Conclusions

Radiation is a treatment modality for pelvic malignancies, which carries significant morbidity and mortality. Radiation cystitis presents with varying degrees of symptoms ranging from dysuria, pelvic pain, and urgency, to severe life-threatening hematuria, small capacity urinary bladder. Treatment of hematuria is according to severity, patient condition, and available modalities for treatment. An individualized and stepwise approach for the management of hematuria to decrease morbidity and mortality, preserve bladder function, and detect complications is advised

Conflicts of interest: None

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