

The use of radiotherapy in the management of follicular cystitis refractory to conservative and surgical management

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Abstract

Follicular cystitis is a proliferative benign lesion which can act locally malignant. Conservative management is best; however, when this fails, surgical resection is necessary up to and including cystectomy in extreme refractory cases. We present a clinical review and our results using radiation in this disease in a woman facing cystectomy.

Introduction

Follicular cystitis (FC) is a rare and non-specific inflammatory disease of the bladder which primarily affects women and is characterized by the presence of lymphoid follicles in the lamina propria of the bladder wall. First described by Cruveilhier in 1856,¹ The diagnosis is made by careful histopathologic review, requiring identification of characteristic follicles in the bladder wall lamina propria, which are classically described as lymphoid follicles containing germinal centers with lymphocytic collars. It has a variable clinical presentation and course and its non-specific nature invoked the following description over 40 years ago, which still holds true today: *Cystitis follicularis is a condition of indefinite etiology and obscure pathogenesis, and prognosis is speculative.*¹

Presentation, symptoms and diagnosis

Follicular cystitis can have a variable presentation but most typically presents similarly to other chronic cystitides with dysuria and increased urinary frequency. Patients are often treated for bacterial cystitis with antibiotics prior to definitive diagnosis by histologic confirmation. Cystoscopic examination may reveal white or pink nodules, often on a background of erythematous mucosa, most com-

monly in the area of the trigone. The lesions may appear granular and solid, nodular, erythematous or edematous on macroscopic pathologic evaluation. Microscopic follicles can also be found in the absence of cystoscopic or gross abnormalities.² A recent publication has shown that FC can be detected cytopathologically in urine specimens.³ Histologically, numerous plasmacytic cells and lymphocytes with lymphoid follicles scattered within the bladder mucosa and submucosa are seen. These are classically described as well-developed lymphoid follicles containing germinal centers with surrounding lymphocytic collars at regular intervals in the mucosa.^{2,3} The overlying urothelium may display mild atypia or metaplasia.⁴

Differential diagnosis

The pathologic differential diagnosis includes malignancies such as follicular lymphoma and other Non-Hodgkin's lymphomas. Additionally granulomatous processes and cystitis with sporadic lymphocytes have similar histologic appearance. Tuberculosis can resemble follicular cystitis at cystoscopy, but can usually be differentiated histologically.⁵

Etiology

Various causative etiologies have been proposed including inflammation and bacterial infection.² Although a causative agent has not been clearly identified, FC is frequently associated with prolonged or repeated urinary tract infections. Salmonella associated cystitis has specifically been implicated.⁶ Most commonly, this is secondary to bladder outlet obstruction or dysfunction, either neurogenic or muscular. Follicular cystitis can also be found adjacent to invasive or in situ bladder carcinomas. It has been suggested that its proximity to carcinomas represents a host response to the bladder tumor. Patients receiving intravesical chemotherapy or intravesical Bacillus Calmette-Guerin therapy have subsequently been shown to develop FC. Rare cases have been reported following pelvic radiotherapy.⁷ Childhood FC can be seen following bladder outlet or urethral obstructive disease and is often accompanied by cystitis cystica. Idiopathic cases of FC have also been seen in biopsy specimens from functioning bladders in the absence of known insult.⁶

Treatment

Patients are often are treated with antibiotics or managed similarly to other chronic cystitides. Treatment with antibiotics, prednisone and vitamin A have been described.³ Therapies similar to those used for interstitial cystitis are also sometimes used, including pentosan polysulfate sodium and dimethyl sul-

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foxide as well as antidepressants such as amitriptyline and duloxetine. Resection can be employed for those patients who develop bulk infiltrative disease causing dysuria or obstructive symptomatology.

Case Report

A 51-year-old white female presented with a multiyear history dysuria and polyuria. Her past medical and surgical history was remarkable for osteoporosis, gastroesophageal reflux, and diverticulosis. Her obstetric/gynecologic history was remarkable for three cesarean sections in three gravid episodes. She had a tubal ligation many years prior, but never has had any significant gynecologic history. Her family and social histories were unremarkable. Her medications included polyethylene glycol, omeprazole, and nabumetone. The family history was without remark.

She was evaluated by serial urinalyses and cultures, none of which revealed significant abnormality. Comprehensive metabolic assay and complete blood count, as well as an erythrocyte sedimentation rate and anti-nuclear antibodies were all within normal limits. A contrast enhanced computed tomography scan of the abdomen and pelvis demonstrated an intravesicular mass-like lesion, which appeared polypoid in nature. The patient was taken to the operative suite where a cystoscopy was performed which revealed a bladder lesion on the anterior bladder wall and bladder dome which was greater than 5 cm in diameter. A trans-urethral resection of bladder tumor (TURBT) was performed which resected all apparent gross disease. Grossly, 3 cm³ of tumor

was identified revealing chronic follicular cystitis with focal foreign body reaction and reactive urothelial atypia. The urinary bladder wall showed significant urothelial edema; however no dysplastic or malignant cells were identified. The slides were reviewed and the diagnosis confirmed at an outside university program specializing in urothelial pathology.

The patient had significant relief, which lasted only a few months. She was subsequently treated with repeat TURBT with a similar finding and a similar postoperative outcome. Steroid therapy over multiple weeks was ineffective as was empiric antibiotic therapy. A final TURBT was performed with gross total resection of 5 cm³ disease with an identical postoperative course. Radiation Oncology was consulted for an opinion as the disease had become so symptomatically crippling that the patient was recommended to undergo palliative cystectomy. A systematic literature review was performed which did not identify previous use of radiotherapy in the management of follicular cystitis, despite the relatively robust history radiotherapeutic efficacy in treating multiple benign conditions.

We discussed with her the paucity of literature regarding the use of radiotherapy for this unusual disease as well as the potential for both long and short term side effects, of low-dose radiotherapy. Informed consent was obtained and a regimen was selected which had been reported as efficacious is the treatment of multiple benign proliferative disorders.⁸⁻¹⁰ Following this, the patient was sent for a final gross resection by TURBT. During this procedure, another 5 cm³ of gross disease was resected with similar findings to the previous. We then delivered external beam radiotherapy to the entire post-void bladder using three-dimensional conformal radiotherapy. The treatment consisted of 600 cGy in 3 consecutive daily fractions of 200 cGy with a 1.5 cm margin around the bladder using 18 MV photons. The radiotherapy was delivered 3 weeks following surgery in consideration of the urothelial edema identified cystoscopically and the previous multiple surgical traumas. The patient tolerated the therapy well and manifested no side effect. She has undergone repeat cystoscopy at her 3, 6 and 12 month follow up visits. The three month visit demonstrated only moderate edematous changes, but the follow-up cystoscopies were completely

normal. She has been absent of symptomatology through her 18 month post treatment visit.

Discussion

Follicular cystitis is an uncommon condition which primarily affects women and is usually treated by observation in its mild form or with anti-inflammatory medications including steroids. Sacral neurostimulation has shown some promise in refractory chronic cystitis,^{11,12} although it is ineffective in 30-50% of patients treated and it is an invasive procedure. In debilitating cases refractory to conservative management, palliative cystectomy including bladder reconstruction has been advocated and is effective,^{13,14} but the long term quality of life following cystectomy with permanent ileostomy or even neo-bladder formation is suboptimal and requires a major reconstructive surgical procedure. Some authors have reported persistence of chronic pelvic pain despite such measures,^{13,14} although the etiology of persistent pain on the absence of the inflamed bladder is unknown.

Conclusions

Follicular cystitis is classically best treated with conservative management such as anti-inflammatory medications and expectant observation. Sacral neurostimulation is also another potentially effective therapy, although it is invasive. However, when conservative management fails, radiotherapy should be considered in lieu of cystectomy in view of the lack of significant untoward side effects and excellent patient tolerance. Further study is required before adopting radiotherapy as a standard of care.

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