Recurring cystitis cystica and cystitis glandularis masquerading as urothelial carcinoma

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We report a rare case of cystitis cystica and glandularis mimicking low-grade urothelial carcinoma that was found incidentally and treated with resection and fulguration via transurethral resection of bladder tumor (TURBT). When early recurrence was found on surveillance cystoscopy 3 months later, the patient was treated with repeat TURBT and intravesical gemcitabine. Surveillance cystoscopy 4 months later revealed cystitis cystica and cystitis glandularis yet again. We highlight the diagnosis and management of multiple early recurrences of cystitis cystica in this patient, particularly our treatment with gemcitabine and close surveillance.

Key Words: benign bladder lesions, cystitis cystica et glandularis, adenocarcinoma, intestinal metaplasia, gemcitabine

Introduction

Cystitis glandularis (CG) is a glandular metaplasia of transitional cells of the bladder resulting from chronic inflammation and irritation of the urothelium from causes, such as infection, calculi, outlet obstruction, or a tumor. The urothelium grows inward into the lamina propia yielding dilated cystic deposits (cystitis cystica) or columnar/cuboidal cells secreting mucin that look like intestinal-type goblet cells (cystitis glandularis with intestinal metaplasia).[1] The epidemiology of CG is unclear as only case reports and retrospective studies of institutional cases have been published. However, Ito et al performed 125 autopsies and reported that CG was found in 40%-92.9% of normal-appearing

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bladders depending on age and gender. CG was found most commonly at the trigone and anterior wall and less frequently on the posterior wall. These benign lesions were found in both males and females with a peak incidence in the fifth and sixth decades of life.[2,3] However, the malignant potential of cystitis cystica and cystitis glandularis (CCCG) has long been considered, and several cases of adenocarcinoma have been reported in CCCG on surveillance.[3] We report a case of early recurrent CG mimicking low-grade urothelial carcinoma that was treated with repeat transurethral resections of bladder tumor (TURBT), cystoscopic surveillance, and intravesical gemcitabine.

Case report

A 57-year-old male with a history of recurrent prostatitis presented to the emergency department at an outside hospital in March 2021 with abdominal pain. Medical history was significant for recurrent prostatitis once every year for the past 10 years. His symptoms of lower back pain, urinary urgency, and frequency resolved with antibiotics and non-steroidal anti-inflammatory drugs each time. He reported an episode of prostatitis 1 month prior to presentation. He reportedly never smoked tobacco but did have an occasional cigar. On review of systems, the patient denied dysuria, hematuria, nausea or vomiting, fever or chills, bone, back or flank pain, and weight loss.

The abdominal pain was attributed to irritable bowel syndrome. However, during the work up, non-contrast computerized tomography (CT) demonstrated bladder wall thickening suspicious for bladder cancer, and the patient was referred to urology.

The CT scans taken at the time revealed irregular thickening of the posterior bladder and a slightly prominent prostate with indentation of the bladder with no hydronephrosis or stones and normal bilateral kidneys. Prior to referral, his initial outpatient cystoscopy in April 2021 reported "3 to 4 papillary tumors on posterior wall of bladder with the largest being 3 cm." The ureteral orifices were not visualized, and the prostate was about 40 grams with bilobar hypertrophy. Urinalysis and urine cytology were negative.

A TURBT with bilateral retrograde pyelogram (RPG) was planned for May 2021. During the TURBT there was about 3.5 centimeters of low-grade appearing papillary tumor over the trigone involving the left ureteral orifice and 1 centimeter of tumor over the posterior bladder wall. These were resected and fulgurated, a left ureteral stent was placed. According to guidelines for suspected intermediate risk urothelial carcinoma, the patient received a single dose of intravesical chemotherapy following the procedure; due to the BCG shortage, 2,000 milligrams of gemcitabine was chosen. Final pathology reports indicated "florid cystitis glandularis of intestinal type with mucin extravasation" and no malignancy, Figure 1. Surveillance was recommended due to a potentially increased risk of adenocarcinoma.

On surveillance cystoscopy in August 2021, persistent inflammation of the trigone, a mound in the midline trigone, and frondular lesions of the right trigone were noted. An abdomen/pelvis MRI demonstrated a polypoid mucosal mass at the posterior bladder wall without muscle invasion. No pelvic lipomatosis was noted on T1-weighted images, nor on the CT scan at initial presentation. A second TURBT with bilateral RPG was completed September 2021, and intravesical gemcitabine was administered in the post-anesthesia care unit. Pathology again reported CCCG with intestinal metaplasia not involving the muscularis, Figure 2. Following discussion, the tumor board was concerned about the high chance of concurrent underlying malignancy undiagnosed by TURBT based on the patient's clinical presentation and rapid recurrence, so full gemcitabine induction was completed December 2021. A colonoscopy and repeat cystoscopy in 3 months were recommended.

During the colonoscopy a 3 mm ascending colon polyp and a 4 mm descending colon polyp were found and removed, and a polypoid mass in the terminal ileum was biopsied and reported as negative for neoplasia. A third TURBT and cystoscopy in March 2022 again revealed CCCG of the posterior bladder wall. Cytology showed clusters of urothelial cells with a differential diagnosis of catheterization and instrumentation versus low grade papillary neoplasm. Ultimately, a follow up cystoscopy 4 months later was negative for any lesions, and the patient has been kept on yearly cystoscopic surveillance due to CCCG's potential association with adenocarcinoma and other malignancies. He remained asymptomatic without any lower urinary tract symptom treatments and was counseled in smoking cessation.

Discussion

This case study highlights a rare instance of CCCG intestinal type with visual appearance of low-grade urothelial carcinoma that had early recurrence within 3 months. To our knowledge, no cases of CG recurring multiple times has been reported, and previously reported cases of CG have not been treated with gemcitabine.

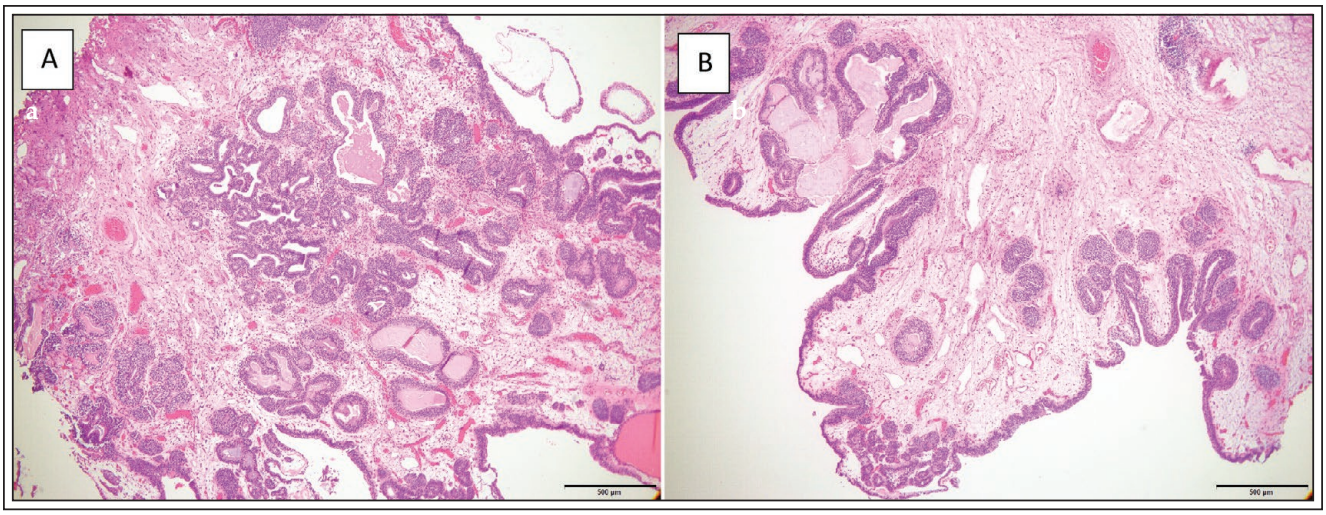

Figure 1. A) Florid cystitis cystica et glandularis without intestinal metaplasia. H&E stain shows florid proliferation of cystically dilated nests with glandular changes. There is edema and mild chronic inflammation in adjacent stroma. The subepithelial cystically dilated urothelial nests with glandular change. The luminally oriented cytoplasm in the cells lining the cystic spaces. The borders are smooth with no evidence of destructive infiltration. **B)** Polypoid cystitis. A polypoid lesion with finger-like architecture lined by benign urothelium and underlying Brunn nest proliferation. Marked edema of the lamina propria, dilated capillaries and rare lymphocytes are noted. Magnification: A-B 40x.

The connection between CCCG and bladder adenocarcinoma is controversial. Ito et al and others have reported CG as a regular finding in normal bladders.[2] CG is found throughout the bladder but most commonly at the trigone while adenocarcinoma is commonly located at the dome or lateral walls suggesting that CG is not a premalignant finding.[2] Their conclusion is that CCCG is found regularly in the bladder without definitive connection to neoplastic changes; if it's asymptomatic, there is no need for

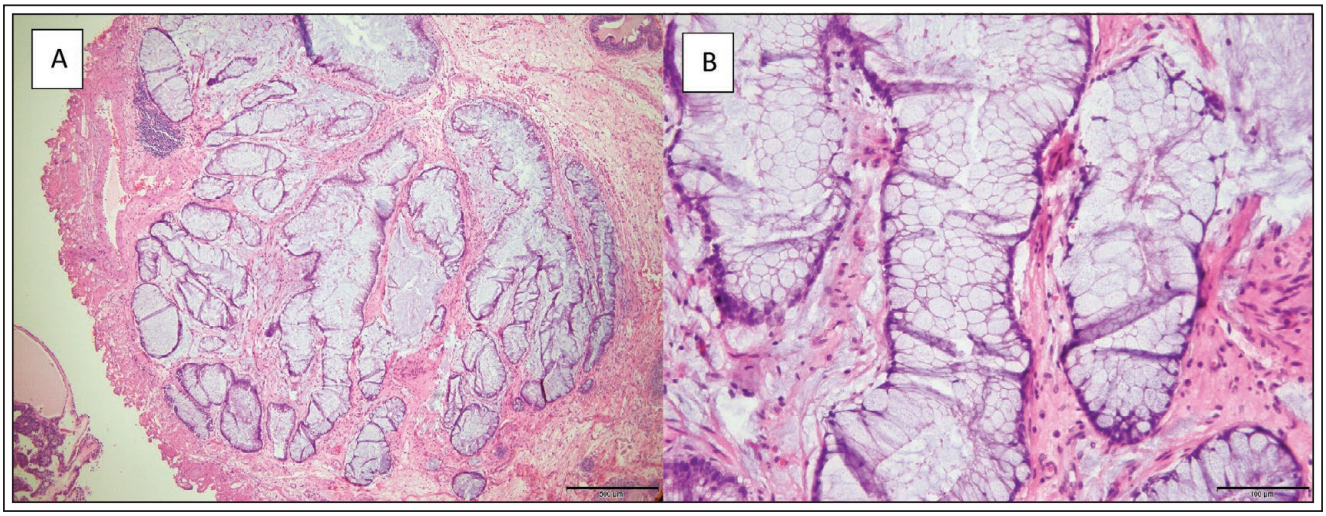

Figure 2. A-B) Florid cystitis glandularis with intestinal metaplasia. Abundant glands lined by goblet cells with abundant intracytoplasmic mucin, resembling intestinal type epithelium. No atypia is present. Gland rupture and extravasated stromal mucin displays no free-floating epithelial elements, signet ring cells or necrosis. Magnifications: A. 40x, B. 200x.

surveillance. Several case series with long term follow up also support this.[4-6]

On the other hand, studies have shown that CG should be monitored regularly with its potential to develop into adenocarcinoma.[3] CG intestinal type is often singled out because it is more often pre-malignant and because it coexists with and looks similar to adenocarcinoma in cystoscopy and on histopathology.[7,8] In one study of 40 cases of cystitis cystica, 8 cases had metaplastic changes; one of those cases with metaplasia also showed dysplasia which progressed to adenocarcinoma.[8] Along with the risk of malignancy, authors have argued that CG should be monitored since it can be a source of ureteral obstruction potentially leading to irreversible kidney injury.[1,9] Additionally, recurrence is quite common although the exact percentage is unclear; recurrence rates range from 5.1% to 59.4% due to small sample sizes.[3,10]

Following this, however, there are mixed opinions on what the optimal surveillance or treatment of CCCG should be. First, identifying and treating the underlying cause of chronic irritation is important. Surgical treatments are recommended to remove any obstructions, decrease symptoms and for pathologic diagnosis (specifically to rule out underlying malignancy). For surveillance, annual cystoscopy and bladder biopsy is commonly recommended.[1] Others recognize a need for monitoring but state that the optimal frequency and duration is unknown.

However, in patients with early recurrence, our case shows that gemcitabine induction may be of benefit to curb continued recurrence of CCCG. With high suspicion of malignancy during both TURBTs, gemcitabine was administered postoperatively during both encounters. Despite the irritative nature of chemotherapeutic agents, the patients remained asymptomatic. Additionally, quarter-yearly cystoscopies (similar to the urothelial carcinoma literature) in the beginning progressing to yearly cystoscopies can detect early recurrence. Close follow up especially in patients with the intestinal type may be of benefit for identifying dysplasia as well identifying and treating ureteral obstruction. A multi-center study of CCCG with large sample sizes is necessary to elucidate exact patient-centered treatment plans through sub-analyses by CG type, whether there are symptoms leading to diagnosis, and time to recurrence. □

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