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Research Article

Cystitis Cystica and Cystitis Glandularis of the Urinary Bladder: A Review and Update

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Abstract

Cystitis glandularis is a proliferative disorder of the urinary bladder which has tended to be associated with glandular metaplasia of the transitional cells that line the urinary bladder. Cystitis glandularis tends to be closely related to cystitis cystica with which it commonly does exist. Cystitis cystica represents a proliferative or reactive changes which tend to occur within von Brunn nests which do acquire luminal spaces and become cystically dilated, and cystitis may undergo glandular metaplasia which does represent cystitis glandularis or the cystitis may undergo intestinal type of metaplasia which is referred to as intestinal type of cystitis. Cystitis cystica and cystitis glandularis is a very common incidental finding. Cystitis cystica and glandularis tend to develop I the setting of chronic irritation or inflammation of the urinary bladder mucosa. Cystitis cystica and glandularis tend to be frequently found in co-existence with interrelated lesions and they represent benign simulators of invasive carcinoma of the urinary bladder. With regard to mode of manifestation and diagnosis, cystitis cystica and cystitis glandularis tend to be diagnosed incidentally based upon: findings of urinary bladder lesions at cystoscopy undertaken for some other reason or upon incidental finding of a urinary bladder lesion following the undertaking of radiology imaging (ultra-sound scan, or computed tomography (CT) scan or magnetic resonance imaging (MRI) scan undertaken for something else. The patient may also manifest with lower urinary tract symptoms of urinary frequency, urgency, urge incontinence or poor flow of urine or difficulty in initiating urine. On rare occasions when the ureteric orifices are involved the patient may manifest with one sided loin pain or bilateral loin pain if both ureteric orifices are obstructed by the urinary bladder lesion. In severe cases of bilateral ureteric obstruction there may be evidence of impairment of renal function. Haematuria could also be a mode of presentation. Ultrasound scan of renal tract could demonstrate a polypoidal thickening of the wall of the urinary bladder usually in the trigone of the bladder but in extensive cases the thickening could be all over the urinary bladder and in cases where the ureteric orifices are obstructed there may be evidence of hydroureter and hydronephrosis. CT scan may show hyper-vascular polypoid mass within the urinary bladder, and MRI scan could demonstrate a hyperintense vascular core with encompassing low-intensity signal. These radiology imaging features are non-specific and would differentiate the urinary bladder lesion from invasive urothelial carcinoma. Diagnosis of the cystitis tends to be made based upon histopathology examination and immunohistochemistry staining studies of biopsy specimens or the trans-urethral resection specimens of the urinary bladder lesions. Microscopy pathology examination of the specimens tend to demonstrate: (a) **a**bundant urothelial von Brunn nests which often tend to exhibit a vaguely lobular distribution of invaginations as well evidence of non-infiltrative growth as well as growth and variable connection to surface, (b) Gland-like lumina with columnar or cuboidal cells with regard to cases of cystitis glandularis, (c) Cystically dilated lumina or cystic cavities which are filled with eosinophilic fluid in the scenario of cystitis cystica, (d) Majority of cases of cystitis tend to demonstrate coexistence of both patterns, (e) Cells lack significant atypia, mitotic activity, stromal reaction and muscular invasion and degenerative atypia tends to be occasionally present. Immunofluorescence studies in cases of cystitis glandularis tend to demonstrate uniform membranous expression of beta catenin without cytoplasmic or nuclear localization. Cases of cystitis cystica and cystitis glandularis tend to exhibit positive immunohistochemistry staining for various markers as follows: GATA3, CK7, (full thickness), CK20 (umbrella cells), p63 (basal cell layer), uroplakin II/III, thrombomodulin, beta catenin, (membranous), and E-cadherin. Cases of cystitis cystica and cystitis glandularis tend to exhibit negative immunohistochemistry staining for the following immunohistochemistry staining agents: CDX2, Villin, MUC2, MUC5AC, and beta catenin, (nuclear). Some of the differential diagnoses of cystitis cystica and cystitis glandularis include: von Brunn nest hyperplasia, Urothelial carcinoma in situ, Inverted Urothelial papilloma, Nested variant of invasive urothelial carcinoma, and Microcystic variant of urothelial carcinoma. On rare occasions cystitis cystica and cystitis glandularis could be found contemporaneously in association with a urothelial carcinoma and hence every pathologist who examines specimens of cystitis cystica and cystitis glandularis needs to undertake a thorough examination of various areas of the bladder lesion to be absolutely

sure there is no synchronous malignancy in the urinary bladder lesion. The treatment of cystitis cystica does entail removal of the source of irritation or source of the bladder inflammation including foreign bodies, long-term urinary catheter, vesical calculus and others as well as trans-urethral resection of the urinary bladder lesion or lesions. On very rare occasions cystectomy had been undertaken. Individuals who have vesical-ureteric obstruction may require insertion of nephrostomy on the side of the obstruction followed by insertion of antegrade or retrograde ureteric stents due to scarring at the site of obstruction or when the scar is too dense then excision of the lesion and re-implantation of the ureter may be required. In cases of severe impairment of renal function, on very rare occasions dialysis may be required as supportive care. But for majority of patients, trans-urethral resection of the bladder lesion would tend to be enough.

Keywords: cystitis cystica; cystitis glandularis; von Brunn nest; histopathology; immunohistochemistry; beta catenin; GATA 3; CK7; CK20; p63; uroplakin II/III; thrombomodulin; E-cadherin; CDX2; villin; MUC2; MUC5AC; trans-urethral resection; benign

Introduction

It has been iterated that cystitis cystica is a terminology which is utilized for a hyperproliferative condition where initial submucosal masses of epithelial cells, termed 'Brunns nests, do undergo cavitation to form fluid-filled cystic structures [1,2]. Cystitis cystica is conjectured to represent a local immune response to a chronic inflammatory stimulus and which has been stated to be associated with recurrent urinary tract infection [1]. It has been stated that when cystitis cystica is present in children, it very rarely does affect the male population. It has been documented that one study by Milošević et al. which had looked at patients who had confirmed cystitis cystica and no concurrent urinary tract abnormality over a 20-year period, of the 127 patients who had been identified [2]. It has been documented that cystitis glandularis does occur when there is metaplasia in a mucous secreting epithelium and it is typified by a central lining of cuboidal or columnar cells [1,3].

It has been stated that cystitis cystica has tended to be an uncommon clinical rare entity in children, and there had been only a handful of reported cases of cystitis cystica in children that had been reported in the literature [1]. In has been pointed out that one study which looked at all paediatric specimens that were taken from the urinary bladder over a 21-year period at the Children's Hospital of Philadelphia, only three patients were identified as having cystitis glandularis [1]. A clinical history for only one of these patients was available a retrospective study of [1], and it had remarked upon a previous bladder exstrophy repair [4]. A small number of individual cases had been published in children over the previous years [5-7].

It has been pointed out that an association had been documented with urinary bladder exstrophy, pelvic lipomatosis and recurrent urinary tract infections in a published article [1,7]. It has been iterated that both cystitis cystica and cystitis glandularis could manifest with irritative lower urinary tract symptoms as well as haematuria [1].

It has been pointed out that the significance of cystitis glandularis in relation to premalignant risk has been the subject of much debate [1]. It has been pointed out that at the moment, even though cystitis glandularis could be found to exist in contemporaneously in conjunction with carcinoma of the urinary bladder, sufficient evidence does not exist currently to confirm that the presence of cystitis glandularis does increase the potential for the future development malignant tumour in the bladder [1,8]. Nevertheless, it has been iterated that the premalignant risk with very widely proliferative cystitis glandularis lesions cannot completely be disregarded or excluded [1,7].

It has been pointed out that at the moment, the treatment of patients who have cystitis cystica does entail utilization of long-term antibiotic prophylaxis for urinary tract infections [2].

It has also been pointed out that for the treatment of cystitis glandularis, transurethral resection of the lesions has generally been the only treatment that has been required [1,7].

It has been explained that cystitis cystica et glandularis (CCEG) represents a benign, proliferative lesion of the urinary bladder mucosa which is typified the von Brunn's nests growing into the lamina propria to become cystically dilated (CC) and metaplastically changing into goblet cells within the mucosa and submucosa of the urinary bladder epithelium (CG) [9,10]. It has been pointed out that all three conditions do commonly coexist and they could be identified within various settings, with the inclusion of normal urinary bladder mucosa, inflammatory diseases, as well as carcinoma [9,11].

Materials

It has been explained that the exact pathophysiology of CCEG is not well understood but it is most likely related to chronic irritation of the urinary bladder mucosa with activation of the humoral immune defence response [9,12]. and it has tended to be associated with recurrent urinary tract infections, chronic bladder outlet obstruction, [13] neurogenic bladder, bladder calculi, or catheterization [8,9].

Interestingly, it has also been documented that pelvic lipomatosis which is an uncommonly rare proliferative condition which causes increased deposition of fat around the urinary bladder, rectum and prostate has tended to be associated with CG, which had been found in up to 75% of patients with pelvic lipomatosis according to a reported article [9,14].

It has been documented that most patients who have CCEG had tended to be asymptomatic, and the lesions usually had tended to be seen incidentally during cystoscopy examination [9]. It has also been pointed out that with regard to symptomatic patients, haematuria, irritative lower urinary tract symptoms, and, rarely, upper urinary tract obstruction has been the commonest manifesting [9]. It has been pointed out that at cystoscopy, florid CCEG often tends to appear as submucosal nodules [8,9]. It has been pointed out that documented cases of CCEG which cause obstruction, albeit without causing irreversible renal injury, had been reported. *Zhu et al.* reported a patient who had CCEG which had caused unilateral ureteric obstruction and acute azotaemia (creatinine, 231 μmol/l) in whom no underlying cause for CCEG was identified. The patient had undergone resection of the 4 cm urinary bladder mass before the renal function returned to baseline levels [9,15].

Demirer et al. reported a case of CCEG which had caused bilateral ureterovesical junction obstruction which had resulted in presentation as renal colic, bilateral ureterohydronephrosis, and haematuria, which was managed by transurethral resection [16].

The association between CCEG and adenocarcinoma of the bladder, which was first reported in 1950, is stated to be controversial [9,17].

Yi et al. recently retrospectively evaluated 166 patients who had CG, and based upon their results concluded that isolated CG does not increase the risk for the development of carcinoma of the urinary bladder [9,18]. In view of this, follow up in the form of repeated cystoscopies had not been warranted. Nevertheless, it has been iterated that in the presence of

dysplasia, long-term clinical follow up with cystoscopies would be required [19].

It has been pointed out that various options of definitive treatment options are available which do range from conservative management to aggressive management. It has also been explained that: the identification of the lesion, treating the lesion, and eliminating the underlying predisposing source of chronic bladder irritation is the most crucial aspect of management of this clinical entity [9]. It has additionally been pointed out that the treatment of this clinical entity does include: the eradication of urinary tract infections with appropriate antibiotic treatment, replacing chronic indwelling urethral catheters with clean intermittent catheterization, or treating urinary bladder calculi [9]. It has also been recommended that symptomatic patients who manifest with bladder outlet obstruction, recurrent haematuria, or obstruction of the ureteric orifices should be managed with transurethral resection of the lesions [9,20].

It has been pointed out that success with these conservative measures tends to be more appropriate for small, focal lesions [9,21].

It has been explained that with regard to patients who experience debilitating symptoms, more invasive and aggressive surgical options would need to be considered [9]. It has additionally been pointed out that patients who have decreased urinary bladder capacity might benefit from a bladder augmentation surgical procedure, and, with regard to patients who have persistent ureteric obstruction, reimplantation of the ureter would be indicated [9,21].

It has additionally been pointed out that radical cystectomy with an orthotopic neobladder represents the most aggressive yet successful surgery which had been undertaken in highly selected cases [9,22].

Although CCEG is regarded as a common benign self-limiting condition requiring minimal intervention in most cases, it may, very rarely, obstruct the upper urinary tracts [9].

Methods

Internet data bases were searched including: Google; Google Scholar; Yahoo; and PUBMED. The search words that were used included: Cystitis cystica of bladder; Cystitis cystica of urinary bladder; Cystitis glandularis of bladder; Cystitis glandularis of urinary bladder; Cystitis Cystica et Glandularis of bladder; and Cystitis Cystica et glandularis of the urinary bladder. Fifty (50) references were identified which were used to write the article which has been divided into two parts: (A): Overview and (B): Miscellaneous Narrations And Discussions From Some Case Reports On Cystitis Cystica.

[A} Overview

Definition / general statements

It has been iterated that proliferative or reactive changes which occur within von Brunn nests that acquire luminal spaces, tend to become cystically dilated and they are referred to as cystitis cystica, and when they do undergo glandular metaplasia, they are then referred to as cystitis glandularis, as well as when they undergo intestinal type metaplasia they are then referred to as cystitis glandularis of the intestinal type [23].

Essential features [23]

The following essential features of cystitis cystica and cystitis glandularis have been summated: [23]

- Cystitis cystica and cystitis glandularis are very common incidental findings.
- Cystitis cystica and cystitis glandularis do develop within the setting of chronic mucosal irritation or inflammation.
- Cystitis cystica and cystitis glandularis tend to be frequently coexisting and inter-related urothelial lesions.
- Cystitis cystica and cystitis glandularis are benign mimics of invasive carcinoma.

Terminology

Clinicians have been reminded that various terminologies have been utilized for cystitis cystica and cystitis glandularis and these include: [23]

- The terminology of cystitis cystica et glandularis have been utilized when combined a combination of features of cystitis cystica and cystitis glandularis are found upon pathology examination.
- Cystitis cystica, the conventional type of cystitis cystica.
- Cystitis glandularis of the intestinal type has been preferentially called intestinal metaplasia.
- The terminology of proliferative cystitis has been used at times but utilization of the terminology of proliferative cystitis is a discouraged terminology which pathologists have been advised not to use.

Epidemiology [23]

- With regard to the epidemiology of cystitis cystica and cystitis glandularis, it has been iterated that both cystitis cystica and cystitis glandularis are extremely commonly encountered and that 60% of normal urinary bladders at autopsy been found to contain cystitis cystica and cystitis glandularis [24].
- It has been stated that cystitis cystica and cystitis glandularis can occur in males as well as in females at any age of life [23,25].

Sites

The sites for the development of cystitis cystica and cystitis glandularis of the urothelium have been summarized to include the following: [23]

- Within the urinary bladder, the urinary bladder neck as well as the trigone of the urinary bladder are the commonest sites to encounter cystitis cystica and cystitis glandularis.
- Cystitis cystica and cystitis glandularis can also be found in the ureters and they tend to be referred to as ureteritis cystica and ureteritis glandularis.
- Cystitis cystica and cystitis glandularis can also be found in the renal pelvis and these lesions in the renal pelvis tend to be referred to as pyelitis cystica and pyelitis glandularis.

Pathophysiology

- With regard to the pathophysiology of cystitis cystica and cystitis glandularis, it has been iterated that cystitis cystica and cystitis glandularis, emanate as a reactive process which does develop in response to chronic irritation, infection, calculi, bladder outlet obstruction of various causes [23,26] including benign prostatic hyperplasia, carcinoma of prostate, urethral stricture as well as catheterization.
- With regard to the pathophysiology of cystitis cystica and cystitis glandularis, the urothelium tends to proliferate as well as invaginate into the underlying lamina propria [23].

Aetiology

- It has been iterated that with regard to the aetiology of cystitis cystica and cystitis glandularis, these lesions ensue chronic irritation / local inflammatory insult of the urinary bladder, ureter, or renal pelvis [23]. Cystitis cystica and cystitis glandularis could also be found in association with bladder exstrophy (ectopia vesicae).

Clinical features

The clinical features of cystitis cystica and cystitis glandularis have been summated as follows: [23]

- Majority of cases of cystitis cystica and cystitis glandularis tend to diagnosed incidentally due to the fact that majority of these lesions tend to be asymptomatic.
- Cystitis cystica and cystitis glandularis may infrequently be the cause for the development of recurrent urinary tract infections in some patients.
- On rare occasions, cystitis cystica and cystitis glandularis do manifest as polypoid or papillary mass that is found during the undertaking of cystoscopy.
- It has been iterated that cystitis glandularis could be associated with pelvic lipomatosis as well as exstrophy of the urinary bladder [23,26].

Diagnosis

With regard to the diagnosis of cystitis cystica and cystitis glandularis, it has been iterated that the diagnosis does rely upon microscopic histopathology examination of resected specimen of the urothelial tissue of the lesion [23].

Radiology imaging features

Fluoroscopy

- Upon intravenous urography, in cases of cystitis cystica or cystitis glandularis, a lobulated outline of the urinary bladder with a nodular filling defect within the urinary bladder would be demonstrated.

Ultrasound scan

Ultrasound scan in cases of cystitis cystica and cystitis glandularis would tend to demonstrate a focal polypoidal wall thickening of the urinary bladder within the area of the trigone but in extensive cases the lesions could be found all over the bladder but these are non-specific findings that are not diagnostic of the lesion.

Computed Tomography (CT) Scan

- It has been stated that CT scan does demonstrate Cystitis cystica and cystitis glandularis lesions as hyper-vascular polypoid masses.

Magnetic Resonance Imaging (MRI) Scan.

- It has been iterated that MRI T2 images of cystitis cystica and cystitis glandularis lesions tend to demonstrate hyper-intense vascular core of the lesion with encompassing low-intensity signal [23,27].
- Ultrasound scan of Renal Tract and Urinary Bladder. ultrasound scan of renal tract and urinary bladder tend to demonstrate cystitis cystica as well as cystitis glandularis lesions of the urinary bladder and even though the features of the lesion would tend not to be specific pathology examination of the lesion which has been biopsied or resected would reveal feature of cystitis cystica or cystitis glandularis. The ultrasound would demonstrate the size and size of the lesion.
- Ultrasound scan of renal tract/urinary bladder would demonstrate if there is any ureteric obstruction with hydroureter plus or minus hydronephrosis.
- Ultrasound would additionally demonstrate the prostate with regard to its size and ultrasonic features.

Prognostic factors

- Cystitis cystica and cystitis glandularis are reactive process without malignant potential [23]
- Cystitis cystica and cystitis glandularis could regress if the cause of irritation is removed [23]

Treatment

Some of the objectives for the treatment of cystitis glandularis include: [23]

- Ensuring elimination of underlying source of irritation
- Provision of antibiotic treatment if the cystitis glandularis is associated with chronic urinary tract infections
- Occasionally surgical resection (trans-urethral resection of the urinary bladder lesion) may be necessary

Cystoscopy Gross description [23,26,28]

- Mucosa may appear grossly unremarkable
- Cystitis cystica appears as translucent submucosal cysts, mostly < 5 mm diameter
- Cystitis glandularis appears as irregular or nodular lesions with a cobblestone pattern or as a polypoid mass

Microscopic (histologic) description [23]

- Abundant urothelial von Brunn nests
    - Often exhibit a vaguely lobular distribution of invaginations
    - Noninfiltrative growth and variable connection to surface
- Gland-like lumens with columnar or cuboidal cells (cystitis glandularis)
- Cystically dilated lumens or cystic cavities filled with eosinophilic fluid (cystitis cystica)
- Majority of cases show coexistence of both patterns
- Cells lack significant atypia, mitotic activity, stromal reaction and muscular invasion [29]
    - Degenerative atypia occasionally present

Immunofluorescence description [23]

- Cystitis glandularis demonstrates uniform membranous expression of beta catenin without cytoplasmic or nuclear localization [30].

Positive immunohistochemistry stains

It has been pointed out that cystitis glandularis of urinary bladder specimens would tend to exhibit positive immunohistochemistry staining for the following immunohistochemistry staining agents: [23]

- GATA3, CK7 (full thickness), CK20, (umbrella cells), p63 (basal cell layer), Uroplakin II/III, thrombomodulin, beta catenin (membranous), E cadherin [30-32].

Negative Immunohistochemistry stains

It has been pointed out that cystitis glandularis of urinary bladder specimens would tend to exhibit negative immunohistochemistry staining for the following immunohistochemistry staining agents: [23]

- CDX2, Villin, MUC2, MUC5AC, beta catenin (nuclear). [30-32].

Differential diagnosis

Some of the differential diagnoses of cystitis glandularis and cystitis cystica have been documented to include the ensuing immunohistochemistry staining agents: [23]

- Von Brunn nest hyperplasia. [23]
    - Urothelial mucosa budding of rounded nests into superficial lamina propria
    - Lacks glandular type epithelium and cystic changes
- Urothelial carcinoma in situ involving von Brunn nests: [23]
    - Prominent cytologic atypia, increased mitoses and apoptotic debris
    - Surface urothelium with carcinoma in situ
    - Trans-urothelial CK 20
- Inverted urothelial papilloma: [23]
    - Architectural complexity; trabecular / corded pattern
    - Periphery of the lesion demonstrates a pushing border
- Invasive urothelial carcinoma, nested variant type. [23]
    - Variably sized nests infiltrating lamina propria and muscularis propria
    - Cytologic atypia in deeper portion of tumour; high Ki67 proliferation rate
    - These tend to be typically, solid rather than cystic or glandular
- Invasive urothelial carcinoma, the microcystic variant of invasive urothelial carcinoma. [23]
    - Variably sized cysts and tubules infiltrating lamina propria and muscularis propria
    - Greater cytologic atypia; higher proliferation rate

[B] Miscellaneous Narrations and Discussions From Some Case Reports On Cystitis Cystica

Bastianpillai et al. [1] reported a 16-year-old boy who did not have any past urological or medical history had presented to his general practitioner with a six-month history of strangury, poor flow of urine, suprapubic discomfort, urinary frequency and urgency. He had also experienced one recent episode of visible haematuria. He did not have any significant family medical history or congenital abnormality noted. The results of his blood tests demonstrated a normal renal function. He had ultrasound scan of his urinary tract which had been ordered in the community, and which had shown two large polypoidal masses that had arisen from the right and left lateral walls of his urinary bladder, that measured up to 2.1 cm and 2.5 cm, respectively. The remainder of his urinary tract was unremarkable, and he did not have any significant post-voiding residual urine volume (see figure 1).

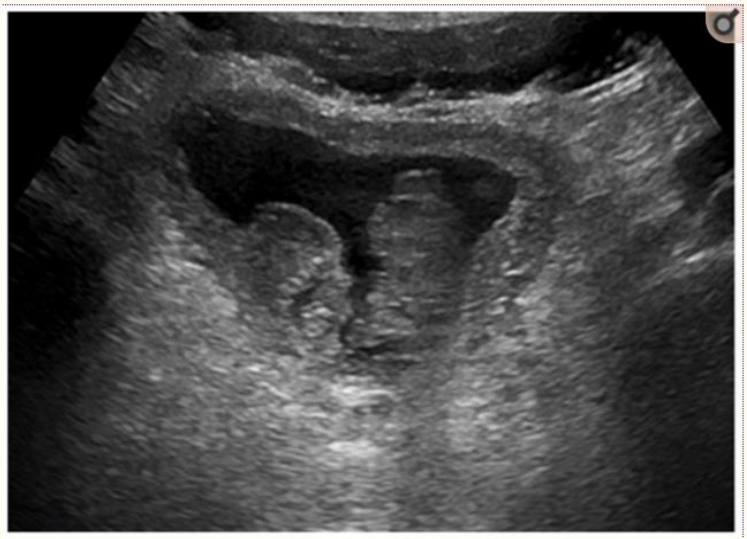

Figure 1: *Trans Abdominal ultrasound of bladder showing two large polypoid masses near bladder neck.*

Reproduced from: [1] Bastianpillai C, Warner R, Beltran L, Green J. Cystitis cystica and glandularis producing large bladder masses in a 16-

year-old boy. JRSM Open. 2018 Mar 8;9(3):2054270417746060. doi: 10.1177/2054270417746060. PMID: 29552345; PMCID: PMC5846953. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5846953/

https://pubmed.ncbi.nlm.nih.gov/29552345/

The patient was next urgently referred to be seen by the urology team. Pursuant to further discussion within the clinic with the patient and his parents, a decision was made to proceed directly to undertake cystoscopy under general anaesthesia for his further assessment and possible resection of these lesions. His urine specimen was sent for cytology examination which demonstrated a few inflammatory cells but no overtly malignant cells within the urine. He had serial urine cultures which did not demonstrate any growth and he had no history of previous urinary tract infections. During his cystoscopy examination, following dilatation of his tight urethral meatus from 14Ch, the two large polypoid lesions were visualized on either side of the neck of his urinary which were partially obstructing, and which simulated malignancy in some areas and inflammatory masses in other areas (see figure 2). The remainder of the urethra was found to be normal. None of the two ureteric orifices was visualised. Both of his urinary bladder lesions were resected using a 17Ch resectoscope, and a small red area upon the posterior wall of his urinary bladder was biopsied. A decision was made to resect most of the lesions from around his urinary bladder neck, leaving as much normal or non-polypoid tissue as possible to reduce the risk of bladder neck stenosis. The patient was kept overnight for irrigation of his urinary bladder, and the catheter was removed the following day with no postoperative complications.

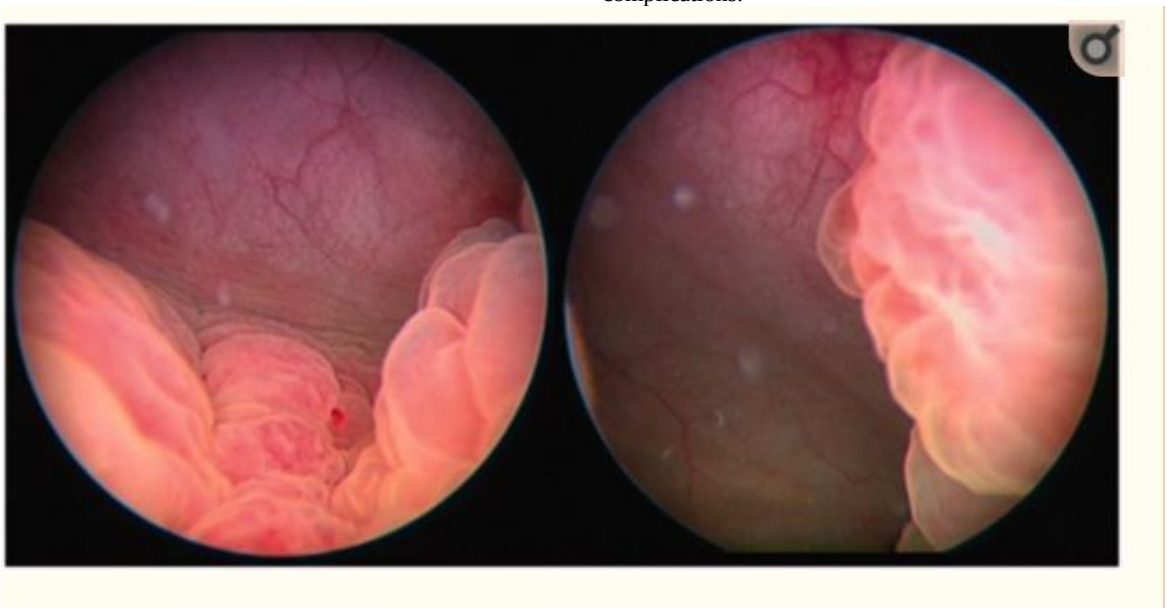

Figure 2: *Cystoscopic views of large polypoid lesions arising from either side of bladder neck.*

Reproduced from: [1] Bastianpillai C, Warner R, Beltran L, Green J. Cystitis cystica and glandularis producing large bladder masses in a 16-year-old boy. JRSM Open. 2018 Mar 8;9(3):2054270417746060. doi: 10.1177/2054270417746060. PMID: 29552345; PMCID: PMC5846953. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5846953/

https://pubmed.ncbi.nlm.nih.gov/29552345/

Histopathology examination of the resected tissue demonstrated features of florid cystitis cystica and cystitis glandularis in all three specimens. Muscle was included in two of the three specimens. No intestinal metaplasia was visualized, and no evidence of dysplasia or malignancy was evident (see figure 3). The patient subsequently had a magnetic resonance imaging (MRI) scan of his pelvis which did not demonstrate any other abnormalities within the pelvis (see figure 4). His lower urinary tract symptoms (LUTS) had subsided one month pursuant to his surgery and his urine flow rate had returned to normal. Pursuant to a multi-disciplinary team meeting discussion, a recommendation was made to repeat cystoscopy on the patient in six months.

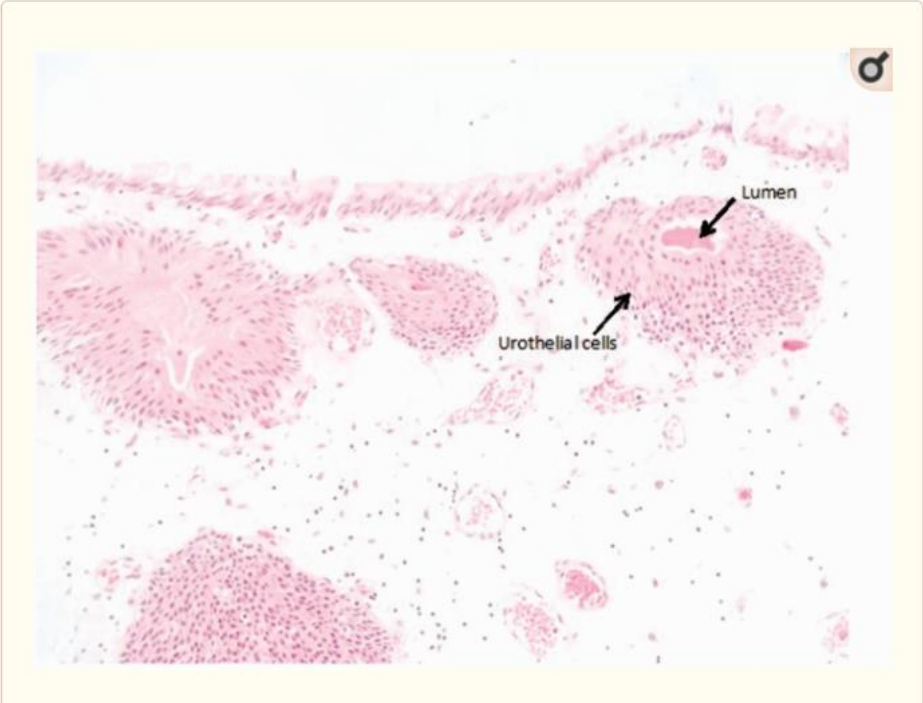

Figure 3

Reproduced from: [1] Bastianpillai C, Warner R, Beltran L, Green J. Cystitis cystica and glandularis producing large bladder masses in a 16-year-old boy. JRSM Open. 2018 Mar 8;9(3):2054270417746060. doi: 10.1177/2054270417746060. PMID: 29552345; PMCID: PMC5846953. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5846953/

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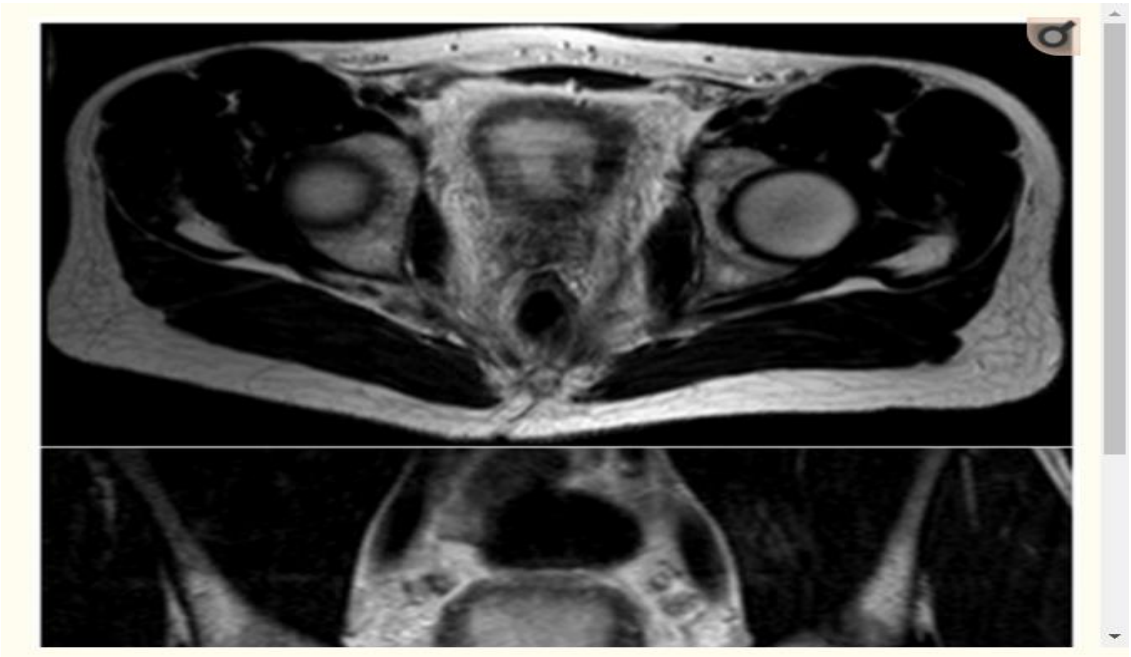

Figure 4:

Reproduced from: [1] Bastianpillai C, Warner R, Beltran L, Green J. Cystitis cystica and glandularis producing large bladder masses in a 16-year-old boy. JRSM Open. 2018 Mar 8;9(3):2054270417746060. doi: 10.1177/2054270417746060. PMID: 29552345; PMCID: PMC5846953. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5846953/

https://pubmed.ncbi.nlm.nih.gov/29552345/

Takizawa et al. [33] made the ensuing iterations related to cystitis glandularis:

- Cystitis glandularis, a proliferative disease of the urinary bladder which tends to be resistant to antibiotics, non-steroidal anti-inflammatory drugs, anti-allergy drugs as well as transurethral resection of the urinary bladder lesion.
- Cystectomy or partial cystectomy had tended to be occasionally required for the treatment of refractory cystitis glandularis.
- It has not been iterated if cystitis glandularis is a premalignant lesion.

Takizawa et al. [33] experienced a case of remission from cystitis glandularis after combination treatment which included: oral treatment with selective cyclooxygenase-2 inhibitor, celecoxib and transurethral resection. Immunohistochemistry staining studies of the bladder lesion showed positive signals of cyclooxygenase-2 in the epithelium of pre-treatment specimens, which had suggested the pathophysiological role of cyclooxygenase-2 in cystitis glandularis. Takizawa et al. [33] did demonstrate the effectiveness of celecoxib against cystitis glandularis for the first time. Takizawa et al. [33] iterated that Celecoxib could be one of the treatment strategies for cystitis glandularis.

Potts and Calleary [34] in 2017, described the rare and not previously documented presentation of cystitis cystica as a large solitary cystic lesion within the wall of a urinary bladder. The patient was a 46-year-old Russian male who had manifested with a history of lower urinary tract symptoms and suprapubic pain. He had a contrast computed tomography (CT) Urogram which demonstrated a 5.8 cm filling defect/cystic mass that was related to the base of his urinary bladder and prostate gland with 8 mm thick wall. He underwent cystoscopy and contrast study of bladder lesion with urethral dilatation and transurethral deroofing of the urinary bladder wall cyst under general anaesthesia. A histology diagnosis of cystitis cystica was made. Potts and Calleary [34] made the following conclusions:

- They had described the rare manifestation of a large solitary urinary bladder cyst which had arisen from the anterior bladder wall, which was diagnosed based upon histopathology examinations as cystitis cystica.
- Cystitis cystica manifesting as a large cystic lesion of the wall of the urinary bladder wall is rare; nevertheless, a diagnosis of cystitis cystica should be considered with regard to unexplained cystic defects of the wall of the urinary bladder.

Smith et al. [35] stated the following:

- Cystitis cystica et glandularis (CCEG) and intestinal metaplasia (IM) had been postulated to represent precursors of adenocarcinoma of the urinary bladder.
- The relationship between these entities and the subsequent development of carcinoma of the urinary bladder had remained unclear.

Smith et al. [35] retrospectively evaluated the association among florid CCEG, IM, and carcinoma of the urinary bladder. They reviewed the clinical records and radiology imaging findings of patients who had a pathology diagnosis of florid CCEG and/or IM for a concurrent or future diagnosis of bladder carcinoma or pelvic lipomatosis. Smith et al. [35] summarized the results as follows:

- They had identified 136 patients from 1982 to 2006 who had florid CCEG of 117 patients or IM of 19 patients.
- Out of the 117 patients who had CCEG, a subset of the patients was identified as having concurrent mucinous adenocarcinoma in 1 patient that amounted to less than 1% of the patients, squamous cell carcinoma in 4 patients which amounted to 3% of the patients, or urothelial carcinoma in 34 patients which amounted to 29 the patients at the time of their initial diagnosis.
- Pure IM was identified contemporaneously with adenocarcinoma of the urinary bladder in 2 patients that amounted to 10%, urothelial carcinoma in 4 patients which amounted to 21% and urothelial carcinoma with glandular differentiation in 1 patient which amounted to 5% of 19 patients.
- Follow-up for 103 patients which had amounted to 75% of the patients had ranged between 7 days and 23.7 years with a median follow-up time of 2.6 years and a mean follow-up time of 4.4 years. Only 1 new case of urothelial carcinoma was identified after 3 months in 1 patient who had CCEG. None of the patients within their series had associated pelvic lipomatosis.

Smith et al. [35] made the ensuing conclusions:

- Both florid CCEG and IM could be identified within benign urinary bladder specimens or contemporaneously with carcinoma of the urinary bladder.
- Even though IM could be associated with a concurrent diagnosis of carcinoma, they had not found any evidence that it does increase the future risk of malignancy and their findings did not support a recommendation for surveillance cystoscopy in such patients.
- They did not find any association between either CCEG or IM and pelvic lipomatosis

Zhu et al. [36] reported a 43-year-old man who had manifested to the emergency room (ER) with a 3-day history of intermittent left flank pain which had lasted several hours at a time that was associated with nausea. He was afebrile and hypertensive with a blood pressure of 173/82 mmHg. He did not have any previous history of visible, kidney stones, trauma or chronic/recurrent urinary tract infections. He was otherwise healthy with a known umbilical and left inguinal hernia, both of which were noted to be reducible upon examination. His initial assessment demonstrated a completely normal examination with no evidence of costovertebral angle tenderness. Social history revealed that he was a body builder who took

creatine supplements daily and smoked 2 to 3 cigarettes per day for the past 5 years.

An urgent ultrasound of his renal tract demonstrated a bladder mass within the trigone (see figure 1a with left hydronephrosis, with left hydroureter and left hydronephrosis. The left ureteric jet could not be demonstrated upon the ultrasound scanning. He then next had a non-contrast computed tomography scan of the abdomen and pelvis which did noy reveal any renal or ureteric calculi to account for the hydroureter. Urinalysis was undertaken which was negative for nitrites or leukocytes; His urine upon cytology examination later came back negative for malignancy. The results of his routine haematology and biochemistry serum blood test results were within was normal range with the exception of a high creatinine of 231 μmol/L (baseline 109 μmol/L in 2005) with a blood urea nitrogen (BUN)/Cr ratio of 37.7, which had indicated acute azotemia. Considering that his pain had resolved and that his serum creatinine had reduced to 206 μmol/L after he had had fluid resuscitation, he was discharged home with the plan for him to undergo an urgent urology follow-up. Three days subsequently, the patient re-presented to the Emergency Room (ER) with ongoing flank pain and for which he was taken to the operating theatre to undergo trans-urethral resection of the bladder tumour (TURBT). His cystoscopy examination demonstrated a large mass which had arisen from his bladder neck, and which had extended along the base of the urinary bladder and which had covered his left ureteric orifice such that the ureteric orifice could not be visualised. The right ureteric orifice was found to be lateral and golf-hole in appearance. The tumour measured over 4 cm in size and it did not exhibit the characteristic appearance of papillary urothelial carcinoma and it did appear to be more solid in nature. The mass was resected completely, down to the base and the area of the resected lesion was fulgurated. The results of his serum creatinine quickly stabilized at 106 μmol/L and he was discharged home in a stable condition, which had suggested that his ureterovesical junction (UVJ) obstruction was the primary reason behind his acute azotemia upon presentation. It was still not clear why the patient went into acute renal failure with obstruction of one renal unit. His hospital chart was reviewed but it did not reveal the use of nephrotoxic medications. The authors conjectured that it was possible; nevertheless, that the sheer mass effect of the lesion, which had traversed the entire base of his urinary bladder, might have also led to a functional obstruction of the contralateral ureteric drainage.

Transurethral resection of the urinary bladder lesion was undertaken to obtain a definitive diagnosis. Pathology examination of the resected urinary bladder lesion demonstrated a 5.1 grams of bladder tissue which depicted an intact urothelial epithelium with underlying oedematous lamina propria. Florid cystitis cystica et glandularis (CCEG), common type, was identified within the lamina propria. The lesion had comprised of many glands that were lined by columnar or cuboidal cells and which were encompassed focally by urothelial cells. There was no evidence of cytological atypia within the lining of the glands found upon histopathology examination of the specimen noted. There was no evidence of intestinal metaplasia or mucin production. Additionally, there was no evidence of dysplasia, carcinoma in situ or papillary urothelial carcinoma.

With regard to the management of the patient, the results of the first biopsy were discussed with the patient, a 3-month post-TURBT cystoscopy examination was undertaken which demonstrated a recurrence of the mass, although to a lesser extent, within the same region of the urinary bladder. The microscopy pathology examination of the bladder tissue of the recurrent lesion did demonstrate morphology features in comparison to the first biopsy. His serum creatinine had once again risen to 132 μmol/L, so he underwent a repeat TURBT was and which demonstrated similar findings as the first operation. The authors, made the ensuing summating iterations:

- They had reported a recurrent case of cystitis cystica et glandularis, common type.
- A normally benign and asymptomatic, CCEG was found to be obstructing the left ureteric orifice, which had led to progressive hydronephrosis of the left kidney with ensuing acute azotemia.
- Despite adequate resection, the lesion recurred within 3 months and had required repeat TURBT.
- The aetiology of CCEG in their reported case was still unclear, even though CCEG tends to be commonly related to chronic irritation.
- While commonly thought of as a consequence to obstruction, CCEG had caused acute azotemia in addition to urinary obstruction in their reported case.
- They believed that their reported case was the first reported case with such specifications

It would be argued that the important messages that should be learnt from this case narration include:

- Clinicians need to aware that CCEG could simulate urothelial carcinoma but the diagnosis can be confirmed based upon pathology examination of the resected urinary bladder lesion.
- CCEG could cause ureteric obstruction with hydroureter and hydronephrosis.
- CCEG could recur pursuant to an apparent complete resection of the urinary bladder lesion and hence urologists need to be vigilant and they should undertake check cystoscopies to ascertain if the lesion which is benign has recurred or not.

Bhana et al. [9] reported a 32-year-old human immunodeficiency virus (HIV)-negative man who was referred to their unit with a 2-week history of bilateral flank pain and nausea. He was upon radiology imaging and laboratory blood testing to have gross bilateral hydroureter and hydronephrosis and a blood serum urea level of 87.5 mmol/l, creatinine 1840 μmol/l and an estimated glomerular filtration rate of 3 ml/min/1.73 m^2. He did not have any significant post micturition residual urinary bladder volume that would suggest a bladder outlet obstruction on ultrasound scanning. The history was additionally considered to be unremarkable, with no preceding history of haematuria, lower urinary tract symptoms, surgical procedures, urolithiasis, or previous urinary tract infections. His clinical examination demonstrated him to be afebrile and normotensive with mild bilateral loin tenderness. Examination of specimens of his urine for urinalysis and culture demonstrated no evidence of urinary tract infection, tuberculosis or schistosomiasis.

Urgent haemodialysis was started, and he underwent cystoscopy which demonstrated extensive cystic and nodular lesions which had involved most of his urinary bladder urothelium, but this was especially prominent at the trigone and bladder neck regions. His ureteric orifices could not be visualized, and retrograde stenting proved to be impossible. Pathology examination of biopsies of his abnormal urinary bladder urothelium demonstrated multiple foci of CCEG (see figure 5) and no evidence of dysplasia, malignancy, tuberculosis, or schistosomiasis was found.

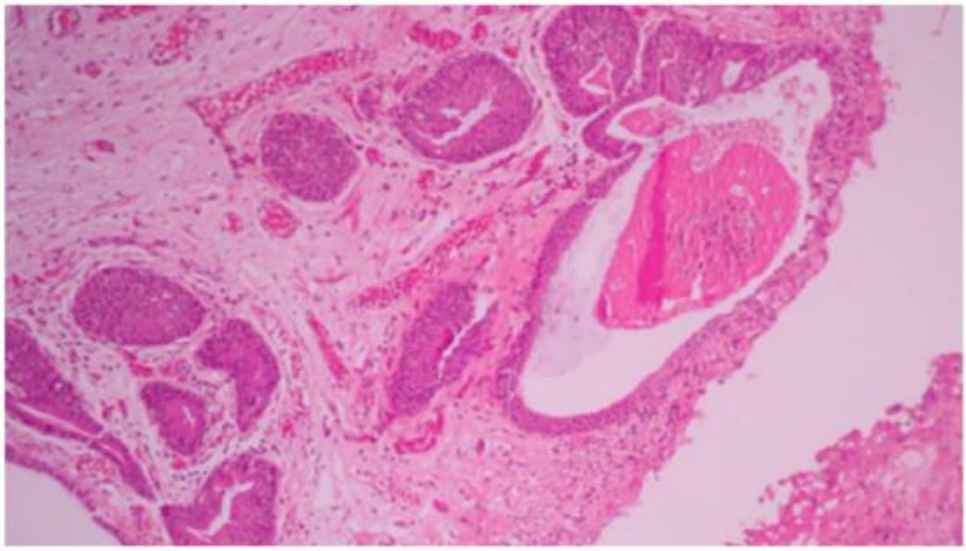

Figure 5: *Photomicrograph of bladder biopsy showing superficial nests of urothelial mucosa with cystic change in the back ground of chronic inflammation.*

Bilateral percutaneous nephrostomies were then inserted, and bilateral anterograde pyelography demonstrated distended ureters with complete obstruction at the level of both vesicoureteral junctions (see figure 6). No filling defects were found that would have been suggestive of concomitant ureteritis cystica were identified. At that stage, the management plan of the authors was to continue with dialysis of the with the bilateral percutaneous nephrostomies in situ and to allow time for the CCEG, which had generally been regarded as a self-limiting disease, to resolve. He had computed tomography (CT) cystogram which demonstrated a good capacity of his urinary bladder, with no evidence of pelvic lipomatosis (see figure 6).

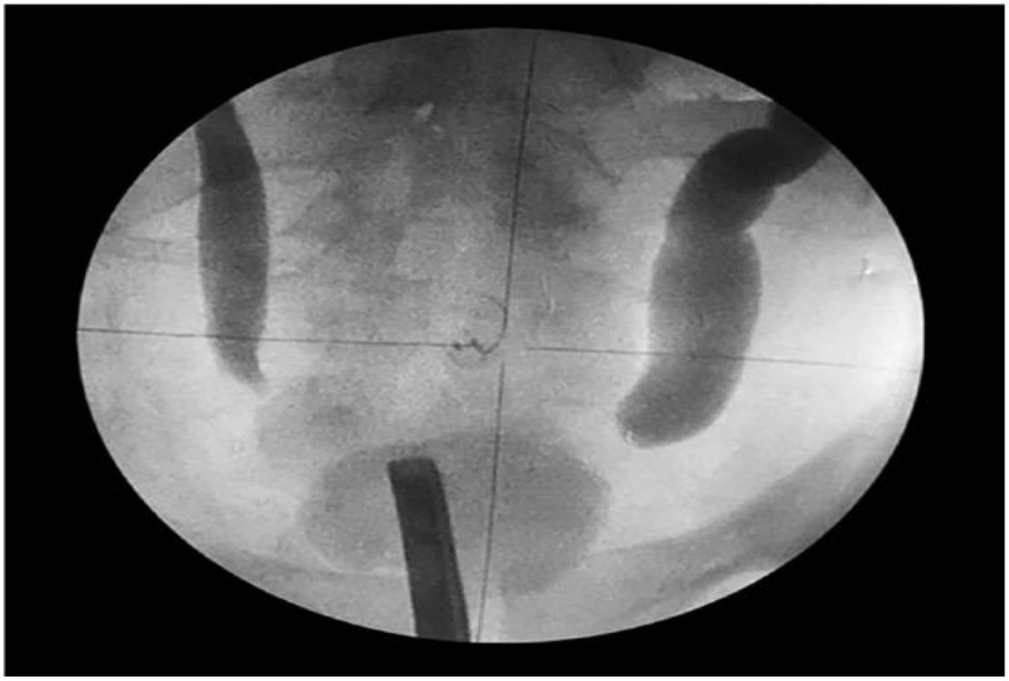

Figure 6: *Anterograde study at the time of cystoscopy showing complete bilateral vesicoureteric junction obstruction with no contrast passing from the ureter into the bladder.*

Reproduced from: [9] Bhana K, Lazarus J, Kesner K, John J. Florid cystitis cystica et glandularis causing irreversible renal injury. Ther Adv Urol. 2021 Jun 10; 13:17562872211022465. doi: 10.1177/17562872211022465. PMID: 34178117; PMCID: PMC8202316. https://pubmed.ncbi.nlm.nih.gov/34178117/ https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8202316/ Copyright © The Author(s), 2021

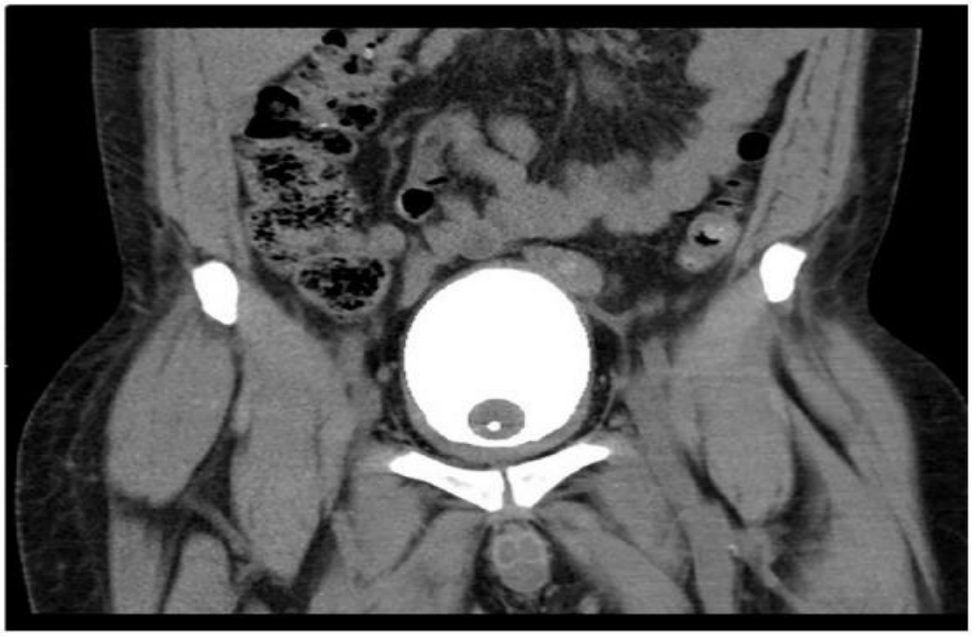

Figure 7: *CT cystogram showing a good capacity bladder with no evidence of pelvic lipomatosis.*

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He had repeat cystoscopy 6 weeks subsequently which demonstrated a marked improvement, with the urinary bladder lesions now limited only to the bladder neck and trigone. Careful resection of the remaining lesions on the trigone was undertaken which exposed slit-like ureteric orifices (see figure 8), but unfortunately, the two identified ureteric orifices could not be catheterised. He had repeat anterograde pyelography which did not show any resolution of the complete obstruction at the lower extent of both ureters.

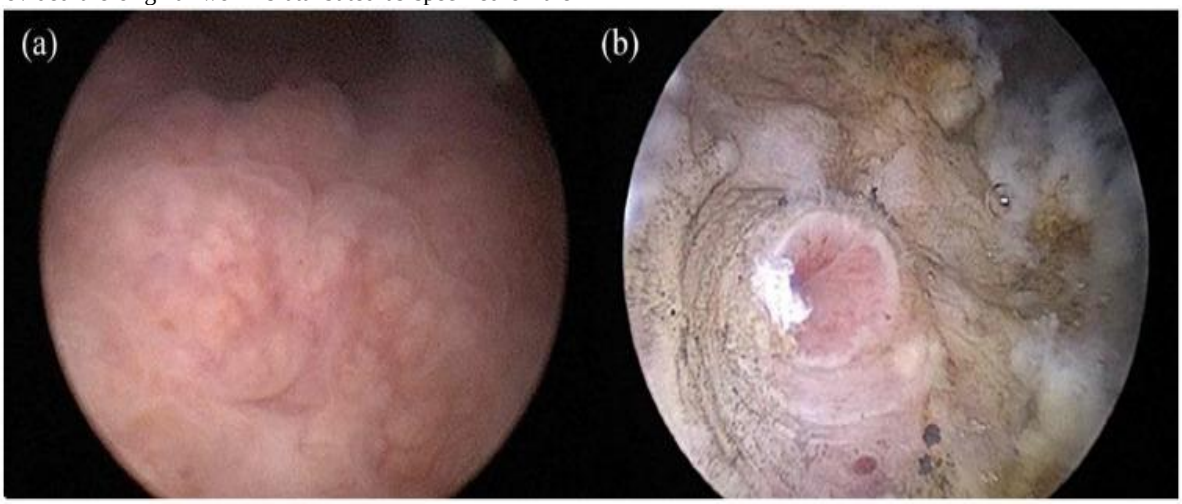

Figure 8: *Cystoscopy view showing nodular lesion over the right ureteric orifice (a) with the slit-like ureteric orifice visible after careful transurethral resection of the bladder lesion (b).*

Reproduced from: [9] Bhana K, Lazarus J, Kesner K, John J. Florid cystitis cystica et glandularis causing irreversible renal injury. Ther Adv Urol. 2021 Jun 10; 13:17562872211022465. doi: 10.1177/17562872211022465. PMID: 34178117; PMCID: PMC8202316. https://pubmed.ncbi.nlm.nih.gov/34178117/ https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8202316/

The patient's serum renal function did not demonstrate any improvement despite the decompressing effect of the bilateral percutaneous nephrostomies. The authors iterated that after they had observed that follow-up cystoscopy had demonstrated resolution of the macroscopic cystic and nodular lesions within the urinary bladder and no lesions were found that would require re-resection, a multidisciplinary decision was made to continue haemodialysis and to place the patient on a waiting list for a renal transplant.

Bhana et al. [9] made the following conclusions:

- Even though CCEG has been regarded as a common benign self-limiting condition that requires minimal intervention with regard to majority of cases, it might, very rarely, obstruct the upper urinary tracts.
- They had presented the first described case in which CCEG had caused bilateral ureteric obstruction and irreversible renal damage.
- Additionally, given that there might be a risk of invasive carcinoma, in cases of CCEG with dysplasia, questions arise about how benign this condition is, whether it needs to be monitored more closely, and what the optimal duration of follow up should be.

A lesson that needs to be learnt from this case report is that CCEG could be associated with bilateral ureteric obstruction and severe renal failure that could require haemodialysis and renal transplantation.

Yi et al. [37] iterated the following:

- Cystitis glandularis (CG) had been postulated to be a potential precursor of adenocarcinoma, even though this postulate has remained controversial.
- Their reported study data was accumulated from 166 cases of cystitis glandularis with follow-up periods that had ranged between 0.5 and 17 years.

Yi et al. [37] retrospectively evaluated the association between intestinal and typical CG and carcinoma of the urinary bladder carcinoma. The patients that were included in their study had manifested with typical CG in 155 cases or intestinal CCG in11 cases between 1994 and 2010. Out of those patients, concurrent carcinoma of the urinary bladder was identified in 15 patients that amounted to 9.0% of the patients, including two cases of squamous cell carcinoma and 1 case of sarcoma of the urinary bladder. The cases of carcinoma were identified either preceding or contemporaneously with the diagnosis of CG. Follow-up was available for 9 out of /11 patients that amounted to 81.8% of the patients who had intestinal CG. Nine months following transurethral fulguration, 8 out of 11 patients that amounted to 72.7% of the patients were in complete remission and 1 patient out of the 11 patients that amounted to 9.1% of the patients had manifested with urinary urgency and dysuria; two patients were lost to follow-up. The follow-up of the patients had ranged from 0.7 years to 4.5 years and their median follow-up was 2.67 years; and their mean follow-up was 2.82 years. During the follow-up of the patients no evidence of subsequent development of carcinoma was identified in any of the patients during the follow-up of both the intestinal and typical CG groups of patients. Additionally, there was no evidence of carcinoma subsequent to CG in either of the typical or intestinal CG groups of patients.

Yi et al. [37] iterated that the results did not support the suggestion that CG does increase the future risk of the development of malignancy in the short term and that they would not recommend repeated cystoscopies over a short period of time.

Velickovic et al. [38] stated that a wide spectrum of glandular epithelial metaplastic changes could be visualised in the bladder and that cystitis glandularis (CG) is a well-known metaplastic lesion which does tend to occur in the presence of chronic inflammation; nevertheless, there are a few data about mucin expression in its two subtypes (typical and intestinal). The purpose of the study of Velickovic et al. [38] was to determine the expression of mucin core proteins and CD10 in the different types of CG. For this examination, they utilized a panel of monoclonal-specific antibodies for MUC1, MUC2, MUC5AC, and MUC6. CG of the intestinal type expressed MUC5AC both in goblet and columnar cells, and strongly expressed intestinal mucin MUC2 only in goblet cells in all cases. Velickovic et al. [38] reported that there was no immunohistochemistry expression of MUC1, MUC6, and CD10 in the metaplastic cells. CG of the typical type exhibited an expression of MUC1 that was similar to normal urothelium; however, the CD10 immunohistochemistry expression was more intensive than in the control group. Velickovic et al. [38] iterated the following:

- The mucin expression profile in the different types of CG does allow the identification of "gastric mucin" (MUC5AC) together with intestinal mucin (MUC2), while typical CG (CGTP) does tend to retain MUC1.
- Different and contrasting immunohistochemistry staining profiles were evident in various forms of CG.
- The absence of CD 10 in CG of the intestinal type is a finding which had pointed towards an incomplete form of urinary bladder metaplasia.

Lee et al. [39] reported a rare case of a 26-year-old patient who had presented with a 3-week history of visible haematuria and suprapubic discomfort. The patients' investigations demonstrated a tumour which had arisen from the wall of the urinary bladder and histopathology examination of the specimen demonstrated features that were consistent with the diagnosis of cystitis glandularis. Their literature review had highlighted the rarity of cystitis glandularis presented in such manner. They suggested that radiographic and endoscopic images could also assist in the future diagnosis of the condition especially in patients in their reported age groups.

Kaya et al. [40] stated that cystitis glandularis is a very rare proliferative disorder of the mucus-producing glands within the mucosa and submucosa of urinary bladder epithelium. Kaya et al reported such a case of glandular cystitis with intestinal metaplasia masquerading as a urinary

bladder tumour in a young male patient who has manifested with severe obstructive urinary symptoms. The patient underwent cystoscopy which demonstrated a well circumscribed, mass that measured 5 ×4 m on the trigone. Transurethral resection of the mass was undertaken and histopathology examination of the resected lesion demonstrated features that were consistent with suggested cystitis glandularis. The literature regarding this entity was been reviewed and the differential diagnosis was discussed. Short-term follow-up of the patient with sonography and cystoscopy showed no recurrence. Kaya et al. [40] made the ensuing summary related to cystitis glanduris:

- Cystitis glandularis is characterized by chronic inflammation and hyperproliferation of bladder mucosa, and contributes to progression of bladder adenocarcinoma.
- TPRG1 (Tumor Protein P63 Regulated 1) is related to cellular inflammatory response, and dysregulation of TPRG1 within tumour tissues as well as it is associated with early recurrence of tumour.
- The effect of TPRG1 on cystitis glandularis was investigated in their reported study.
- In the first instance, urinary bladder specimens were isolated from patients who had cystitis glandularis and *E. coli*-induced cystitis rat. Expression of TPRG1 was found to be up-regulated in the bladder specimen. Furthermore, adeno-associated virus (AAV)-mediated silence of TPRG1 was delivered into rat, and data from haematoxylin and eosin (H and E) staining demonstrated that injection with AAV-shTPRG1 ameliorated *E. coli-had* induced histology changes within urinary bladder tissues of rats, and had suppressed the inflammatory response.
- Secondly, TPRG1 was also increased within primary cystitis glandularis cells. Knockdown of TPRG1 had decreased cell proliferation of primary cystitis glandularis cells, as well as had suppressed the migration.
- Thirdly, cyclooxygenase-2 (COX-2) was up-regulated within the urinary bladder specimen isolated from patients who had cystitis glandularis and *E. coli*-induced cystitis rat. Injection with AAV-shTPRG1 had reduced protein expression of COX-2, p65 and prostaglanodin E2 (PGE2) in the urinary bladder specimen.
- Finally, interference of COX-2 attenuated TPRG1 over-expression-had induced increase of cell proliferation and migration in the primary cystitis glandularis cells.

Kaya et al. [40] concluded that TPRG1 had promoted inflammation and cell proliferation of cystitis glandularis via the activation of NF-κB/COX2/PGE2 axis.

Hong et al. [41] made the ensuing iterations:

- Cystitis glandularis has tended to be characterized by chronic inflammation and hyperproliferation of bladder mucosa, and it does contribute to progression of adenocarcinoma of the urinary bladder.
- TPRG1 (Tumor Protein P63 Regulated 1) is related to cellular inflammatory response, and dysregulation of TPRG1 within tumour tissues and it is associated with early recurrence of tumour.
- The effect of TPRG1 on cystitis glandularis was investigated in their reported study.

With regard to the method of their study, Hong et al. [41] reported the following: Firstly, they had isolated urinary bladder specimens from patients who had cystitis glandularis and *E. coli*-induced cystitis rat. With regard to the results, Hong et al. [41] reported the following:

- They had found out that the expression of TPRG1 was up-regulated within the urinary bladder specimen.
- Additionally, adeno-associated virus (AAV)-mediated silence of TPRG1 was delivered into rat, and data from haematoxylin and eosin (H and E) staining demonstrated that injection with AAV-shTPRG1 ameliorated *E. coli*-induced histopathology changes within the urinary bladder tissues of rats, and had suppressed the inflammatory response.
- Secondly, TPRG1 was also found to be increased in primary cystitis glandularis cells.
- Knockdown of TPRG1 had decreased cell proliferation of primary cystitis glandularis cells, and had suppressed the migration.
- Thirdly, cyclooxygenase-2 (COX-2) was found to be up-regulated within the urinary bladder specimens that were isolated from patients with cystitis glandularis and *E. coli-i*nduced cystitis rat.
- Injection with AAV-shTPRG1 did reduce protein expression of COX-2, p65 and prostaglandin E2 (PGE2) within the urinary bladder specimen.
- Finally, interference of COX-2 attenuated TPRG1 over-expression-induced increase of cell proliferation and migration in the primary cystitis glandularis cells.

Hong et al. [41] concluded that TPRG1 had promoted inflammation and cell proliferation of cystitis glandularis via activation of NF-κB/COX2/PGE2 axis.

Qu et al. [42] investigated the relationships of urinary bladder mucosal inflammatory factors, interleukin-1 (IL-1), interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α) with the occurrence and development of cystitis glandularis (CG), and their effects upon the prognosis of patients. With regard to the methods, Qu et al. [42] reported that a total of 61 patients who had CG from January 2010 to 2014 were randomly selected and tissue specimens of postoperative patients were collected. 16 cases of normal urinary bladder mucosa during the same period were obtained as a control group. Blood specimens and fresh tissue specimens had been collected from 6 patients who had CG. The messenger ribonucleic acid (mRNA) levels of IL-1, IL-6 and TNF-α were detected by means of a reverse transcription polymerase chain reaction (RT-PCR). The protein levels of IL-1, IL-6 and TNF-α in serum of patients who had GC and normal controls were detected through an enzyme-linked immunosorbent assay (ELISA). The protein expressions of IL-1, IL-6 and TNF-α were ascertained via immunohistochemistry (IHC), and their relationships with the clinical features and prognosis of GC were analysed. A Cox proportional hazard regression model was utilised for multivariate analysis on the prognostic factors of CG, and all the tests were undertaken with 95% confidence interval (CI). Qu et al. [42] summarised the results as follows:

- The protein expressions of IL-1, IL-6 and TNF-α in patients with CG were found to be obviously higher than those in normal group. The mRNA levels of IL-1, IL-6 and TNF-α in the serum of patients with CG were also significantly higher than those in normal group ($P<0.05$).

- The expressions of IL-1, IL-6 and TNF-α in CG were positively correlated.
- TNF-α was found to be an independent prognostic factor of CG.

Qu et al. [42] made the following conclusions:

- IL-1, IL-6 and TNF-α are were found to be associated with the occurrence and development of CG.
- TNF-α does present as an independent prognostic factor of CG that can be used for the diagnosis of cystitis glandularis.

Qiu et al. [43] evaluated the safety and efficacy of trans-urethral front-firing photo-selective vaporesection for the treatment of cystitis glandularis, by comparing the procedure with the trans-urethral bipolar plasmakinetic resection. With regard to the methods of the study, Qiu et al. [43] reported that from January 2014 to July 2016, 41 patients who had pathology examination diagnosed cystitis glandularis in their hospital, were divided into two groups which included the following: Twenty two (22) cases had undergone trans-urethral front-firing photoselective vaporesection which constituted the observation group, and the other 19 cases had undergone transurethral bipolar plasmakinetic resection which represented the control group of patients. All of the patients were regularly treated with postoperative intra-vesical instillation chemotherapy with utilization of pirarubicin. The clinical data of two groups were statistically analysed in order to compare the differences of the safety and efficacy of the treatment options. Qiu et al. [43] summarized the results as follows:

- All of the surgeries were undertaken successfully.
- There were no statistical significances with regard to the peri-operative data, the operation time, the decreased concentration of haemoglobin (Hb)and Na+, operative related complications, indwelling catheter duration and hospitalization duration between the two groups.
- The first-time cure rate and the effective rate of trans-urethral front firing photo-selective vaporesection was shown to be significantly better in comparison with those of transurethral bipolar plasma kinetic resection ($P<0.05$ for each).

Qiu et al. [43] concluded that comparing the traditional trans-urethral bipolar plasma kinetic resection for the treatment of cystitis glandularis, trans-urethral front firing photo-selective vaporesection with postoperative intravesical instillation chemotherapy with pirarubicin, was found to be a safer, simpler, and more effective method, which could be a new optional method of treatment of cystitis glandularis within the conditional hospitals, deserving the worthy of clinical popularization.

Zouari et al. [44] reported a 22-year-old man, who did not have any past medical history, who had consulted in emergency for acute urinary retention and left renal colic. Bladder catheterization was undertaken as well as an ultrasound scan which showed left obstructive pre-meatus calculi of 6 mm and distension of his urinary bladder. Upon examination the patient was found to be afebrile and a slight tenderness on the left flank was found upon his abdominal palpation. Upon digital examination (DRE), Zouari et al. [44] found an enlarged prostate gland; there were no indurations and no areas of softness or tenderness within the prostate gland found during the examination. An anti-inflammatory and antalgic treatment was provided to the patient. After one week, Zouari et al. [44] removed the urethral catheter but the patient was still having dysuria. Another ultrasound scan was undertaken; there was an inflammatory aspect of the bladder noted with a thickened bladder wall and a tissular proliferation that measured 5*2 cm on the bladder neck and at the left wall with large implantation and probably prostate infiltration. It was vascularized on color Doppler ultrasound scan (see figure 9, and figure 10). Meanwhile, the patient had developed another episode of acute urinary retention few weeks subsequently. His biological examinations were normal. Urine His Urinalysis was normal. His serum prostate specific antigen (PSA) level was about 1.6 ng/ml. He had magnetic resonance imaging (MRI) scan which demonstrated a pseudo-tumoral urinary bladder wall thickening which was associated with vesical floor budding with prostate median lobe infiltration (see figure 11 and figure 12). The patient was admitted for an endoscopic examination which was undertaken on March, 9th, 2016 and the examination demonstrated an inflammatory aspect of the bladder mucosa as well as a solid mass within the neck of the urinary which had arisen from the prostate gland most likely. It was difficult to determine the origin of the mass, whether it was from the prostate gland or from the urinary bladder. Cystoscopy was undertaken and a biopsy of the presumed mass was taken for pathology examination. Pathology examination of the mass that was biopsied during the cystoscopy revealed features that were considered as conclusively diagnosing a glandular cystitis without any features of malignancy (see figure 13). During the follow up assessment of the patient, he still had dysuria as well as urinary incontinence/leakage. He had ultrasound scan six months later which demonstrated an enlarged prostate gland of 60grams volume, and his post void residual volume of urinary bladder urine was 280ml and he was also found to have bilateral hydronephrosis. The patient was admitted to hospital again in March 2017 and a second cystoscopy was undertaken. The cystoscopy examination revealed that the prostate gland was obstructive with a median lobe. A trans urethral resection of the median lobe of the prostate gland was undertaken. Pathology examination of the resected median lobe of the prostate confirmed features of a benign prostate hyperplasia (see figure 14 and 15).

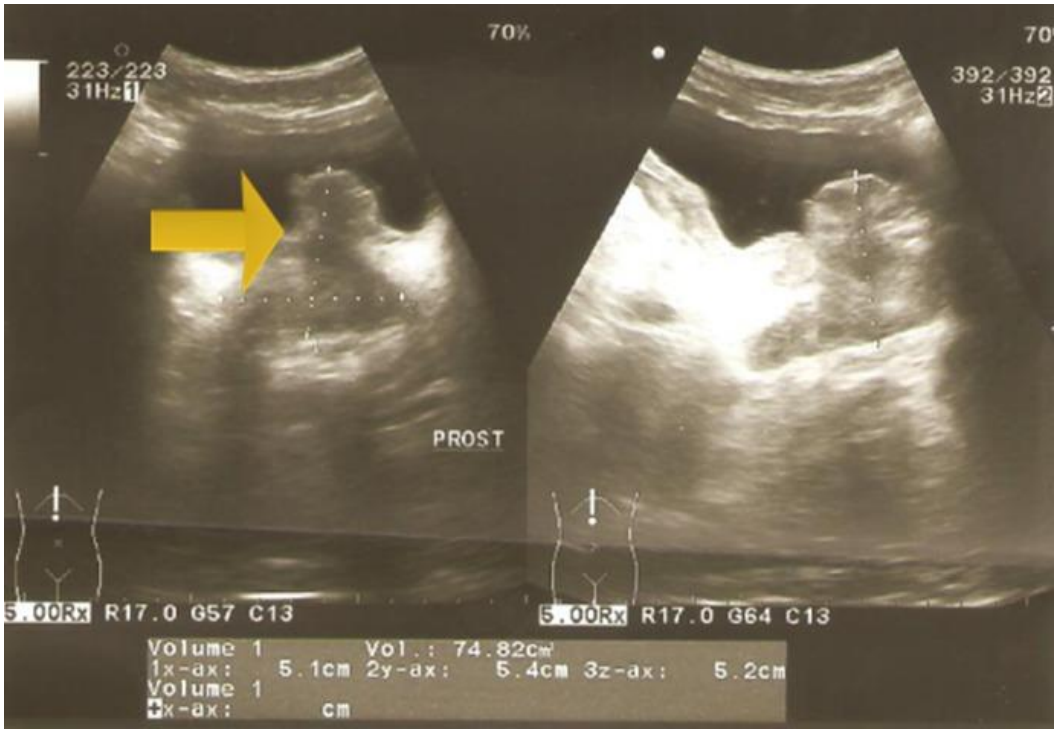

Figure 9: *Bladder wall thickness*

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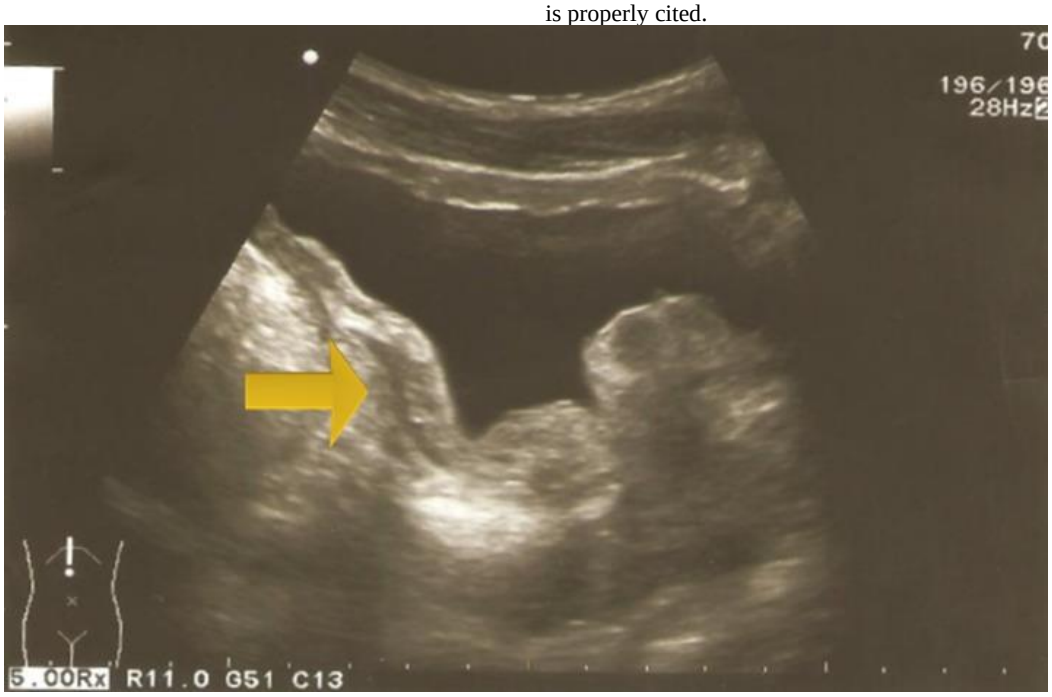

Figure 10: *Enlarged prostate of 60 grams.*

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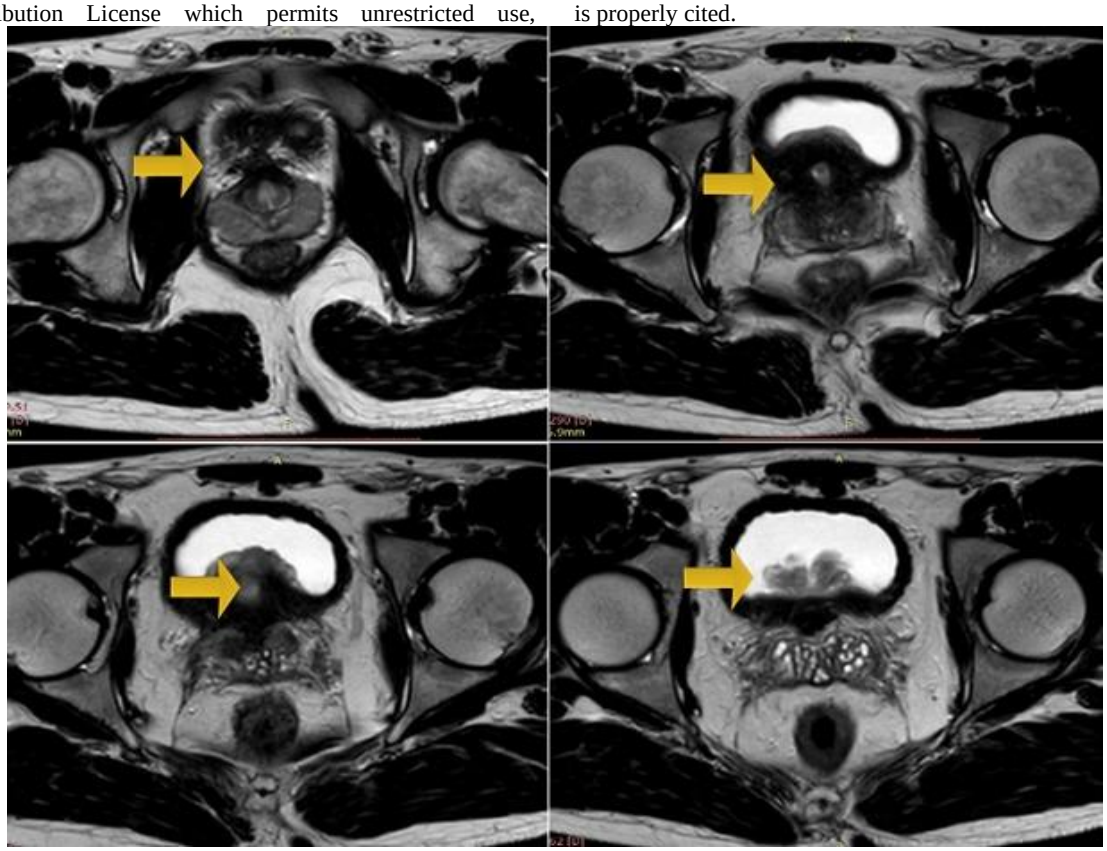

Figure 11: *Axial T2 weighted sequence showed an enlarged prostate gland associated with a lobulated lesion arising from the cystic floor.*

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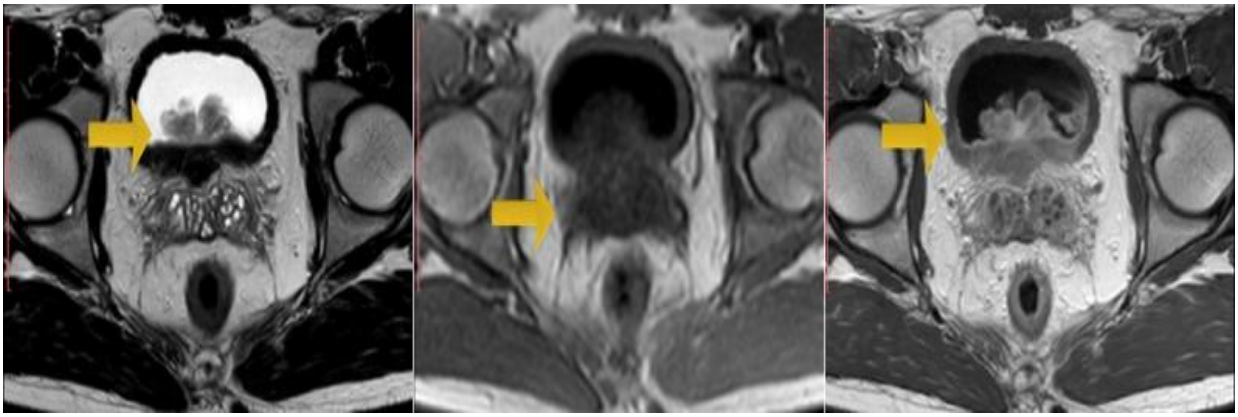

Figure 12: *The bladder floor mass presents as a low signal mass on T1, heterogeneous signal on T2 with central branching hyperintensity. This central hyperintensity showed an avid enhancement on contrast administration and represents the vascular stalk. These findings are evocative of Cystitis glandularis.*

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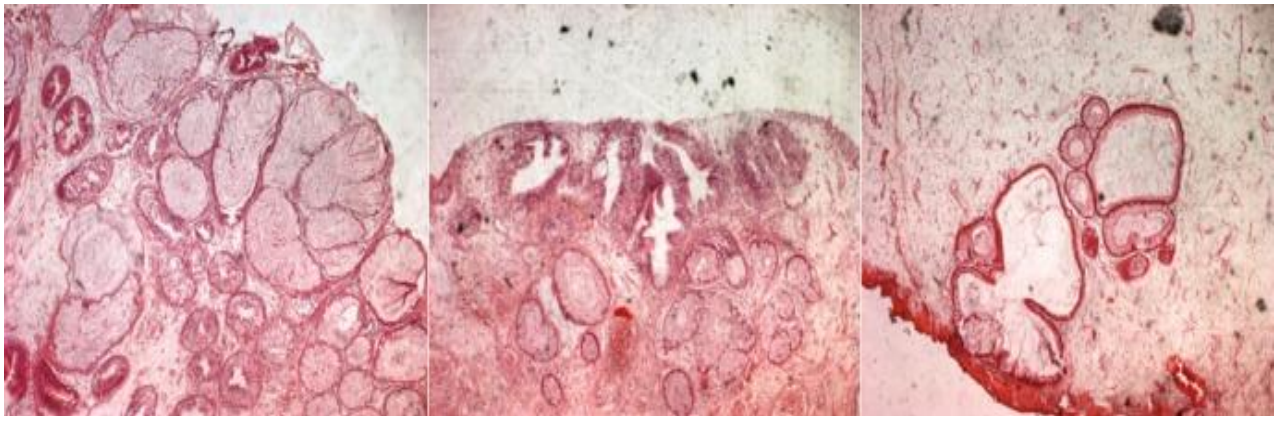

Figure 13: *The lesions consisted of a proliferation of glands in the lamina propria, lined by columnar epithelium, with mucin production. There was no significant nuclear hyperchromasia, pleomorphism. (H-E x 40).*

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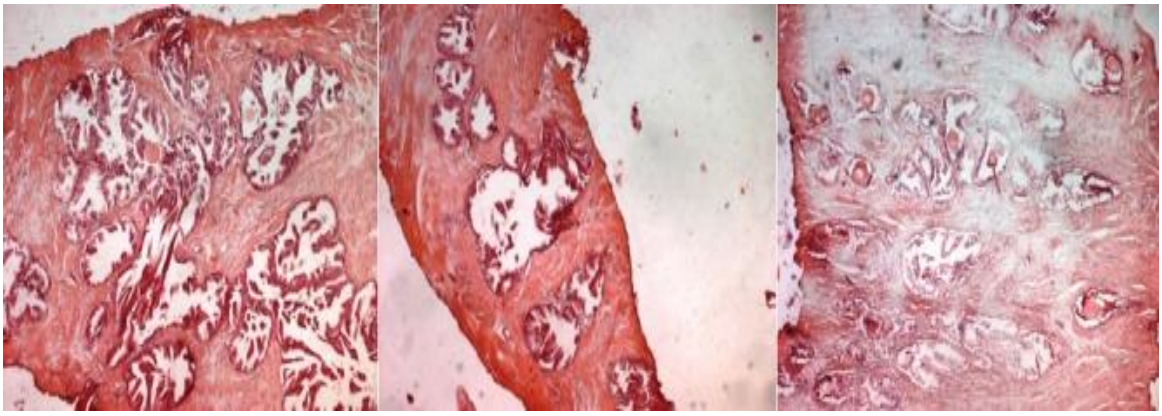

Figure 14: *Benign prostatic hyperplasia involving both glands and stroma. The hyperplasic glands are, well differentiated, crowded, separated by stroma, with corpora amylacea in the lumens (H.E x 40).*

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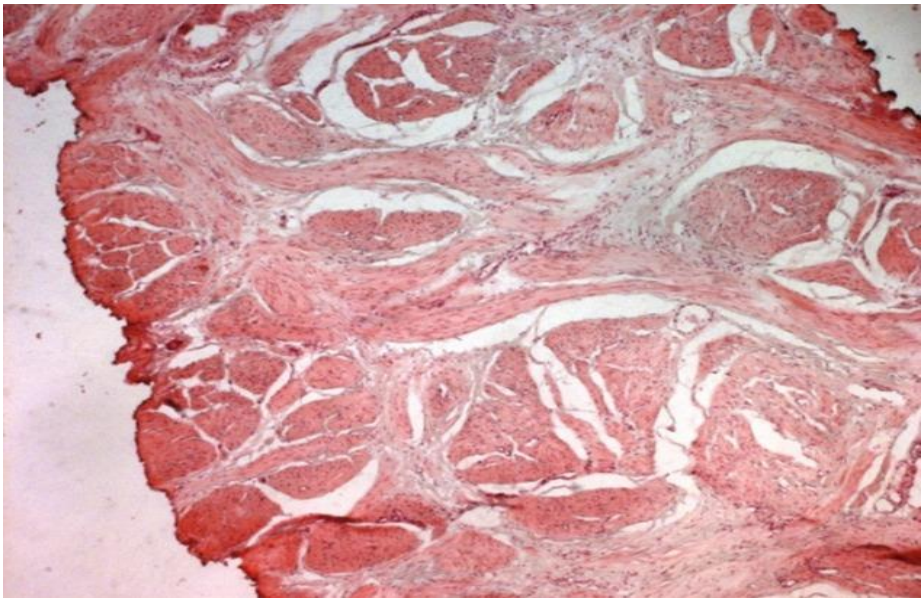

Figure 15: *Low power view of an area of stromal hyperplasia with bundles of smooth muscle. (H.E x 40).*

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Mo et al. [45] made the following iterations:

- Pelvic lipomatosis (PL) is a rare benign condition which tends to be associated with characteristic overgrowth of histologically benign fat and invasion and compression of pelvic organs, which often tends to lead to non-specific lower urinary tract symptoms (LUTS).
- About 40% of patients who have do have cystitis glandularis (CG).
- The cause of PL combined with CG is poorly understood, and at the time of publication of their article, there was no effective treatment.
- Refractory CG with upper urinary tract obstruction even does require the undertaking of partial or radical bladder resection.

Mo et al. [45] reported a patient who was suffering from PL with CG and who was treated by means of transurethral resection of bladder tumour (TUR-BT) and oral administration of celecoxib, a selective cyclooxygenase-2 (COX-2) inhibitor. The LUTS of the patient were alleviated, and the cystoscopy results improved significantly. Immunohistochemistry staining studies of the resected urinary bladder mass demonstrated up-regulated COX-2 expression in the epithelium of the TUR-BT samples, which had suggested that COX-2 might participate in the pathophysiological process of PL combined with CG.

Mo et al. [45] concluded that they had reported for the first time that celecoxib might be an effective treatment strategy for PL combined with refractory CG.

Zhou et al. [46] stated the following:

- Cystitis glandularis (CG) is an unusual proliferative disorder of the urinary bladder.
- Increasing evidences had demonstrated that long non-coding RNAs (lncRNAs) do play pivotal roles in a variety of cellular progresses.
- Nevertheless, there are rarely reports related to the role and underlying molecular mechanism of lncRNAs in CG.

In their study, Zhou et al. [46] firstly isolated the primary cells from the tissues of CG and adjacent normal tissues, and they found that UCA1 was up-regulated in the primary CG cells (pCGs). Then, Zhou et al. [46] demonstrated that knock out of UCA1 had reduced the cell viability, had inhibited the cell proliferation and had restrained the migration potential and overexpression of UCA1 promoted that in pCGs. Additionally, Zhou et al. [45 new 46] had demonstrated that UCA1 had played its role through sponging of the miR-204 in pCGs. Furthermore, Zhou et al. [46] illustrated that miR-204 exerted its function through targeting CYCLIN D2 (CCND2) 3′UTR at mRNA level in pCGs. Ultimately, Zhou et al. [46] revealed the role and regulation of UCA1/miR-204/CCND2 regulatory axis in pCGs. In summary, Zhou et al. [46] stated that their study, for the first time, had illustrated the role and underlying mechanism of an-lncRNA UCA1 in CG, providing a potential biomarker and therapeutic target for human CG.

Hu et al. [47] stated that majority of patients who have cystitis glandularis (CG) do suffer from recurrence after treatment of the primary lesion. Hu et al. [47] undertook a multi-centre study to clarify the recurrent risk factors and constructed a predictive nomogram for the risk of recurrence. Also, Hu et al. [47] tried to investigate the correlation between CG and bladder cancer. With regard to the methods of the study, Hu et al. [47] reported the following:

- Consecutive patients who had pathologically confirmed CG were divided into training and validation sets.

- The clinicopathological characters were collected from electronic medical records of the patients.
- Uni-variate and multivariate logistic regression analyses were utilised to identify independent risk factors of CG recurrence in the training set.
- The predictive nomogram was developed by incorporating these independent factors and histological subtype.
- The performance of the nomogram was assessed and validated with respects to its calibration, discrimination, and clinical usefulness.
- The risk of developing subsequent bladder cancer was analysed from the follow-up data.

Hu et al. [47] summarized the results as follows:

- Ultimately, 278 eligible patients had been included in the study and they were allocated to a training set which included 190 patients and a validation set which included 88 individuals.
- Out of them, 165 patients which amounted to 59.35% of patients experienced CG recurrence, and none of them had shown evidence of subsequent bladder carcinoma during a median (IQR) follow-up time of 27 months during which the follow-up had ranged between 14 months and 57 months.
- The results of multivariate analysis revealed that urinary infections, long-term indwelling catheter usage, urinary calculus, squamous metaplasia, and atypical hyperplasia were independent risk factors for CG recurrence.
- The C-index (95% CI) of the nomogram was found to be 0.76 (0.69–0.83) within the training set and 0.72 (0.61–0.83) within the validation set. A decision curve analysis (DCA) demonstrated that this predictive nomogram was clinically useful.

Hu et al. [47] made the following conclusions:

- They had developed as well as they had validated a nomogram to predict the individualized risk of CG recurrence.
- Also, they had demonstrated that neither intestinal nor typical CG had increased the consequent risk of bladder cancer during the follow-up period.

Li et al. [48] stated the following:

- Cystitis glandularis (CG) is a proliferative disorder of the urinary bladder which tends to be characterized by transitional cells that have undergone glandular metaplasia.
- The underlying mechanism associated with this transformation has been poorly understood.

With regard to the methods of their study, Li et al. [48] reported that they had compared the expression of messenger RNA (mRNA) and long non-coding RNA (lncRNA) from normal bladder mucosa and CG using microarray analysis. They utilized the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis to describe molecular interactions. Li et al. [48] summarised the results as follows:

- Microarray analysis had identified 809 significantly dysregulated mRNAs in CG tissues; 606 were up-regulated and 203 were down-regulated (greater than 2-fold difference in expression from normal tissue, $P<0.05$).
- KEGG pathway analysis had shown that the mRNAs that co-expressed with lnc-RNAs were enriched in the cell cycle regulation pathway.
- They had identified four up-regulated lncRNAs (ENST00000596379, ENST00000463397, NR 001446 and NR 015395 in the coding-non-coding co-expression (CNC) network analysis as being associated with the expression of four mRNAs (SMAD3, ORC1, CCNA2 and CCNB2).NR 015395 was revealed to be a competing endogenous RNA (ceRNA) of miR-133a-3p that targets SMAD3.

Li et al. [48] conclude their study was the first work to measure the expression of dysregulated lncRNA and ceRNA in CG and identify the crosstalk between mRNA and lncRNA expression patterns in the pathogenesis of CG.

Garg et al. [49] studied the manifestation and natural course of cystitis cystica et glandularis. Garg et al. [49] undertook a retrospective analysis of patients who had histopathology examination confirmed cystitis cystica et glandularis from March 2016 to March 2018 who at least HAD completed their 2 years' follow-up assessments. They included in the analysis the perioperative details along with the last available follow-up records. Garg et al. [48 new 49] summarized the results as follows:

- A total of 10 patients were included in the study.
- The mean age (± standard deviation) of the patients was 33.4 (±14.0) years and nine of the patients that amounted to 90% of the patients were men.
- The most common manifestation of the patients was urinary storage and voiding lower urinary tract symptoms which were reported by 80% of the patients along with haematuria which was reported by 40% of the patient and dysuria which was reported by 20% of the patients.
- Four patients that amounted to 40% of the patients had the presence of hydronephrosis in their pre-operative radiology imaging, of which three patients that amounted to 30% of the patients had bilateral mild hydroureteronephrosis.
- All the 10 patients underwent transurethral resection of the bladder tumour as all as they were diagnosed as having urinary bladder mass on their pre-operative radiology imaging.
- All of the 10 patients had a trigonal lesion with a bullous appearance which was partially obstructing the bladder neck.
- Six patients that amounted to 60% of the patients had undergone insertion of double J in the perioperative period.
- The mean (± standard deviation) duration of their follow-up was 32.8 (±7.5) months.
- Patients were kept on regular surveillance with radiology imaging and cystoscopy as was indicated.
- Eight patients that amounted to 80% of the patients had developed recurrence within the follow-up period. The mean number of recurrences was 1.5 (±1.1).
- One of the patients did undergo augmentation ileocystoplasty with bilateral ureteric reimplantation in view of the recurrent lesion with a small contracted urinary bladder, while another patient had undergone cystectomy with urinary diversion as a

result of recurrence and refractory lower urinary tract symptoms.

- Apart from the aforementioned findings and scenarios, there was no evidence of malignancy after the treatment of cystitis cystica et glandularis in any of the patients.

Garg et al. [49] made the following conclusions:

- Cystitis cystica et glandularis is a rare clinical pathology entity which often simulates urinary bladder tumour.
- Cystitis cystica et glandularis is common in men and it often manifests with lower urinary tract symptoms.
- Transurethral resection of the urinary bladder lesion does form the mainstay of treatment of cystitis cystica et glandularis.
- Nevertheless, Cystitis cystica et glandularis often tends to be associated with upper renal tract hydronephrosis.
- Its controversial premalignant nature compounded with recurrence and risk of upper tract deterioration do warrant close surveillance.

Hong et al. [50] stated the following:

- Cystitis glandularis has tended to be characterized by chronic inflammation and hyperproliferation of bladder mucosa, and does contribute to progression of adenocarcinoma of the urinary bladder.
- TPRG1 (Tumor Protein P63 Regulated 1) is related to cellular inflammatory response, and dysregulation of TPRG1 within tumour tissues and tends to be associated with early tumour recurrence.
- The effect of TPRG1 upon cystitis glandularis was investigated in their reported study.
- Firstly, urinary bladder specimens were isolated from patients who had cystitis glandularis and *Escherichia Coli (E. coli)*-induced cystitis rat.
- They found that the expression of TPRG1 was up-regulated in the urinary bladder specimens.
- Moreover, adeno-associated virus (AAV)-mediated silence of TPRG1 was delivered into rat, and data from haematoxylin and eosin (H and E) staining had shown that injection with AAV-shTPRG1 ameliorated the Escherichia Coli (E. Coli)-induced histopathology changes within the urinary bladder tissues of rats, as well as it had suppressed the inflammatory response.
- Secondly, TPRG1 was also increased within primary cystitis glandularis cells. Knockdown of TPRG1 had decreased cell proliferation of primary cystitis glandularis zcells, and had suppressed the migration.
- Thirdly, cyclooxygenase-2 (COX-2) was found to be up-regulated within the urinary bladder specimens that were isolated from patients who had cystitis glandularis and Escherichia coli- (*E. coli)*-induced cystitis rat. Injection with AAV-shTPRG1 had reduced protein expression of COX-2, p65 and prostaglandin E2 (PGE2) within the urinary bladder specimen.
- Lastly, interference of COX-2 attenuated TPRG1 over-expression-induced increase of cell proliferation and migration in the primary cystitis glandularis cells.

Hong et al. [50] concluded that TPRG1 had promoted inflammation and cell proliferation of cystitis glandularis through activation of NF-κB/COX2/PGE2 axis.

Conclusions

- Cystitis cystica and cystitis glandularis are benign lesions that tend to be diagnosed frequently incidentally or they may manifest with non-specific urinary tract symptoms, recurrent urinary tract infection or loin pain due to obstruction of the ureter which could emanate in impairment of renal function.
- Radiology imaging and cystoscopy examination would demonstrate the urinary bladder lesions but the findings tend to be non-specific.
- Histopathology examination and immunohistochemistry staining studies of specimens of the bladder lesions that are obtained by biopsy or resection of the lesion would confirm the diagnosis as well as confirm whether the cystitis is alone or there is a synchronous urinary bladder malignant tumour.
- Treatment of cystitis cystica does entail complete resection of the urinary bladder lesion as well as ensuring contributory causes and sources of bladder irritation and inflammation are removed.
- Rare cases of cystitis cystica and cystitis glandularis that are associated with obstruction of the ureter and hydronephrosis as well as impaired renal function may require insertion of nephrostomy to improve upon the general condition of the patient before providing surgical resection of the bladder lesion.
- Cystitis cystica and cystitis glandularis are benign lesions that tend to simulate urothelial carcinoma.

Conflict of Interest – None

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