Original Article

Incidence of adenocarcinoma bladder in patients with cystitis cystica et glandularis: A retrospective study

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ABSTRACT

Introduction: Cystitis cystica et glandularis (CCG) is a hyper proliferative condition, likely representing a local immune response to chronic inflammatory stimulus. It has been hypothesized as a potential precursor of adenocarcinoma; however, a definite association has not been demonstrated. We aimed to determine whether CCG is a precursor to malignancy and to study the correlation of its two histological variants: the typical and the intestinal metaplasia (IM) type CCG.

Materials and Methods: In this retrospective study, all the cases of CCG diagnosed and treated between January 2012 and December 2019 were analyzed. All the cases were followed up cystoscopically and biopsies were taken if the lesion persisted. The development of adenocarcinoma during the follow-up was noted. The patients were divided into two groups based on the histological subtype, i.e., the typical type and the IM type, and the two groups were also compared in terms of presentation, cystoscopic appearance, and development of adenocarcinoma.

Results: A total of 64 patients, with 52 in the typical and 12 in the IM group were analyzed. The commonest symptom was hematuria (59.38%), followed by irritative bladder symptoms (51.56%). The median follow-up period was 5 years and 5 months (range: 7–96 months) and no patient progressed to adenocarcinoma. On comparing the two groups, the lesions weresignificantly more extensive in the IM group (50% vs. 15.38%). However, there were no differences in the symptoms or the development of malignancy between the two groups.

Conclusions: At a median of 5 years and 5 months of follow up, CCG (including the IM-type) did not show any increase in the risk of malignancy.

INTRODUCTION

Cystitis cystica (CC) is a hyper proliferative condition affecting the bladder mucosa, in which the submucosally invaginated masses of transitional epithelial cells, also called the "Brunn's nests" undergo cavitation to form fluid-filled cystic cavities.[1] However, when these transitional cells lining the cystic cavities undergoes metaplasia to a columnar cell type then the condition is termed as Cystitis Cystica et Glandularis (CCG).[1] CCG is of two histological types; the typical type with no mucus secretion and the cavities being lined by simple columnar cells, and the intestinal metaplasia (IM) type wherein the simple columnar epithelial cells are replaced by mucin-secreting goblet cells.[2]

CCG is commonly encountered in the clinical practice and has been considered as an anatomical variant, being reported in 60%–70% of the autopsy series.[2,3] However, it has been believed that these lesions represent a local immune response to a chronic inflammatory stimulus such as recurrent urinary tract infections, prolonged catheterization, chronic bladder outlet obstruction etc.[4] CCG is mostly asymptomatic and detected incidentally or at times may present with

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irritative lower urinary tract symptoms, hematuria, and occasionally hydroureteronephrosis.[5] Some of these lesions, especially the intestinal type, when widespread, may mimic adenocarcinoma on the cystoscopic examination.[4] Not just the cystoscopic findings, but the actual progression of CCG to adenocarcinoma of the bladder was first demonstrated by Immergut and Cottler,[6] thereafter others have also reported a similar association.[7-9] Such an association has been refuted more recently.[10,11] However, these studies are plagued by either a small number or a short period of follow-up. Hence, in this retrospective study, we evaluated our institutional data with an aim to determine whether CCG in general and the IM subtype in particular, has an association with adenocarcinoma of the urinary bladder.

MATERIALS AND METHODS

We reviewed the records of all the patients who were diagnosed with CCG between January 2012 and June 2019; however, the follow-up records of all these patients were reviewed till December 2019. Patients whose follow-up data were missing were excluded from the study. All individuals provided written informed consent for undergoing cystoscopy and biopsy and a consent for using their medical records for research and publication even at a later date. The procedures adhered to the ethical guidelines of Declaration of Helsinki and its amendments and the authors confirm the availability of, and access to, all the original data reported in this study.

The patient's demographics, comorbidities, presenting complaints were recorded from the case records. The findings of preoperative ultrasound of the kidney, ureter and bladder were recorded. The diagnosis of CCG was made on transurethral resection and biopsy of the lesions. The biopsy was performed using a 24 Fr bipolar resectoscope using 0.2 mm, 30° resection electrode loop (Olympus). During this transurethral resection, the entire lesion was resected if possible. If the complete resection was not possible, then the leftover lesions were fulgurated. The cases were further divided into two groups based on the histopathological finding. Group I consisted of patients with typical CCG, where the cystic cavities were lined by columnar epithelial cells within the lamina propria of the bladder, while those with IM type of CCG, where the simple columnar epithelial cells were replaced by mucin-secreting goblet cells, were clubbed into Group II [Figures 1 and 2]. In cases where both forms coexisted, the patient was grouped into the type which was predominant.

As per the institutional protocol, all the patients with CCG were kept on a 6 monthly follow-up for the first 2 years and then on annual follow-ups. At each of these follow ups, the patients were subjected to clinical examination, urine cytology, ultrasound of kidney ureter, and the bladder and cystoscopy. Cystoscopies were performed under local anaesthesia. Biopsy was taken if a lesion was found on these surveillance cystoscopies. If no lesion was detected on the cystoscopy, then the patient was kept only on cystoscopic surveillance as per the protocol. The follow up data including the results of the repeat biopsies were recorded.

During the follow-up, the records were specifically looked for the resolution of symptoms; resolution of lesions on cystoscopy and the result of the repeat biopsies for the progression of these lesions into adenocarcinoma of the bladder. We then carried out a comparison between the two groups to assess for any differences between the two types of CCG.

The data were compiled into a Microsoft Excel worksheet and analyzed using statistical software Statistical Package for Social Sciences (SPSS) version 24.0 (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, version 24.0. Armonk, NY, USA: IBM Corp). Categorical data were compared using the Student's *t*-test while the Chi-square test was used to compare the nominal variables between the two groups. $P < 0.05$ was considered to be statistically significant.

RESULTS

Seventy-four patients were diagnosed with CCG during the study. Of these, 8 patients had either no follow-up records or defaulted on the follow-ups after the few initial ones and hence were excluded. Two patients were excluded because their initial histopathology reports were missing, and they could not be assigned to a particular group. Hence, the records of a total of 64 patients were finally analyzed.

As summarized in Table 1, the mean age of the patients was 35.625 years. All the patients in our study group were males. Gross hematuria was the most common presenting symptoms followed by increased frequency of micturition and dysuria. Eight patients (5.12%) had

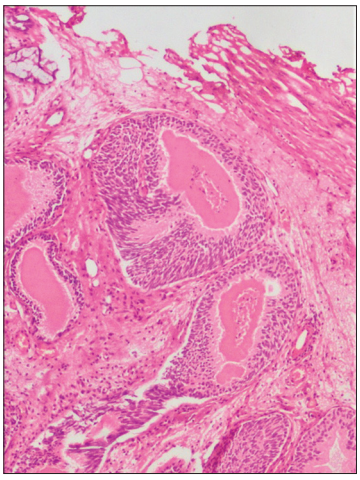

Figure 1: Cystitis cystica et glandularis showing a typical columnar lined subepithelial glandular metaplasia

Table 1: The demographic profile and the clinical findings in the study population

Attributes	Values, *n* (%)
Total patients of CCG	64
Age (years), mean (range)	35.625 (24-48)
Hematuria	38 (59.38)
Increased frequency	33 (51.56)
Dysuria	31 (48.44)
Hydroureteronephrosis	8 (5.12)
Recurrent UTI	2 (2.56)
Co-morbidities	7 (10.94)
Smokers	20 (31.25)
Follow-up, mean (range)	4 years 9 months (7 months-8 years)
Resolution of symptoms	32 (50)
Complete resolution of lesions	15 (23.43)
Increase in the size of lesions	4 (6.25)
Decrease in the size of lesions	34 (53.13)
Lesions remaining static in size	11 (17.19)
Progression to adenocarcinoma (*n*)	0

CCG=Cystitis Cystica et Glandularis, UTI=Urinary tract infection

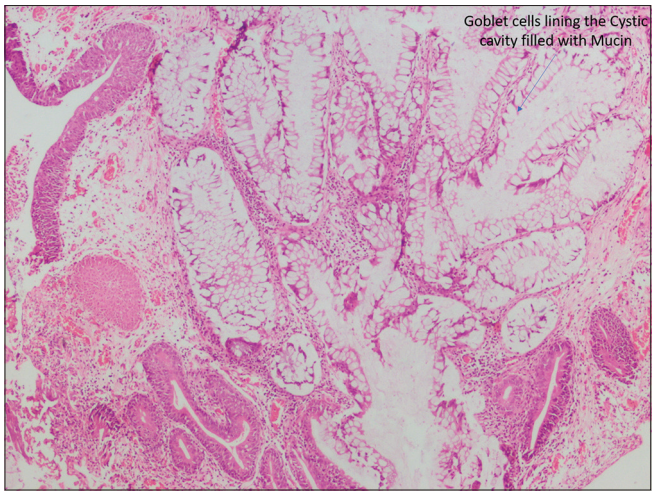

Figure 2: Cystitis cystica et glandularis with intestinal metaplasia showing metaplasia of the columnar lined cells into goblet cells with mucin

hydroureteronephrosis at presentation. None of our patients were detected incidentally and all had presented with one or more symptoms which warranted further evaluation thus leading to the diagnosis. Only two out of the total 64 patients (2.56%) had a history of recurrent urinary tract infections (pus cells on urine microscopic examination and positive urine cultures during the follow-ups). They were treated with culture-specific short course antibiotics before taking up for cystoscopy.

Four patients had associated diabetes mellitus (well controlled on oral hypoglycemics), three had hypertension which was well controlled on a single drug and 20 patients were smokers.

Preoperatively, ultrasound could pick up nodular lesions or focal thickening of the bladder wall in 52 patients (81.25%). The other 12 patients were diagnosed only on cystoscopy. These 12 patients had hematuria as one of their presenting symptoms and hence were taken up for cystoscopy. On cystoscopy, the lesions were mostly papillary with a broad base. The trigone was involved in all the 64 (100%) patients with extensive lesions extending beyond the trigone in only 14 (21.88%) patients. The ureteric orifices were obscured on cystoscopy in all of these 14 patients, which included the 8 patients who had associated hydroureteronephrosis. During the follow-up period of the study, a total of 398 cystoscopies and 317 biopsies were performed, on the 64 patients adhering to the protocol of 6-monthly cystoscopy for the first 2 years followed by annual cystoscopy and biopsy if the lesion was still present.

On histopathology, 12 patients (18.75%) had IM type CCG while the rest 52 (81.25%) had the typical type CCG.

The mean follow-up period was 4 years 9 months (median: 5 years 5 months). The lesions resolved completely in 6 (9.38%) patients after the initial transurethral resection, and in 09 (14.06%) more patients, the lesions regressed completely after subsequent resections/fulgurations over a mean follow up period of 63 months. In four patients, the lesions progressed during the follow-up and one of them developed hydroureteronephrosis at a later date while under follow up. Two out of these four patients had typical type of CCG at the initial diagnosis, but the lesions changed to IM type on the follow up biopsies. These 2 patients who had a change (after 5 years of the initial diagnosis for the 1st and 4 years for the second patient) in the biopsy findings on follow up were analyzed in the typical type group, as per the initial group assignment. The lesions reduced in size but did not regress completely in 34 (53.13%) patients, while it remained almost of the same size in 11 (17.19%) patients. The symptoms resolved in 32 (50%) patients, which included 13 in whom the lesions had regressed completely, over a mean follow-up of 55 months. None of the 64 patients had any evidence of adenocarcinoma development during the follow-up period.

The two groups, i.e., the IM group and the typical type CCG group were comparable in terms of age, comorbidity profile, and the duration of follow-up [Table 2].

There was no significant difference between the two groups as far as the presenting complaints were concerned, however the number of patients with extensive lesions on the initial cystoscopy was significantly higher in the IM group ($P = 0.0089$). In the follow-up period, the resolution of symptoms and the regression of lesions on cystoscopy were also similar in both the groups.

DISCUSSION

CCG is a proliferative disorder of the bladder urothelium. When the urothelium formed by transitional cells invaginates

Table 2: Comparison between the two groups

Attributes	IMCCG	Typical CCG	Test of significance	*P*
Total number	12	52	-	-
Mean age (years)	35.08	35.75	t=−0.28496	0.388
Presentation, *n* (%)				
Hematuria	8 (66.67)	30 (57.69)	χ^2=0.3255	0.568
Dysuria	5 (41.67)	26 (50.0)	χ^2=0.2711	0.602
Frequency	8 (66.67)	25 (48.08)	χ^2=1.3491	0.245
HDUN	3 (25.0)	5 (9.62)	χ^2=2.1099	0.146
Cystoscopic finding of extensive lesions beyond the trigone	6 (50.0)	8 (15.38)	χ^2=6.836	0.0089
Follow up				
Duration of follow-up (months)	62.27	56.26	t=0.68303	0.248
Resolution of symptoms	8 (66.67)	24 (46.15)	χ^2=1.641	0.200
Complete resolution/regression of lesions on follow-up cystoscopy	10 (83.33)	39 (75)	χ^2=0.3773	0.539

CCG=Cystitis Cystica et Glandularis, IMCCG=Intestinal Metaplasia type CCG, HDUN=Hydroureteronephrosis

into the lamina propria, these invaginated cluster of cells are termed as Brunn's nests. At times these Brunn's nests become cystically dilated thereby forming what is referred to as CC. Only when these cystically dilated central lumen is lined by glandular epithelium it is referred to as CCG.[1] CCG is of two types: Typical type, wherein the lumen is lined by columnar epithelium without any mucin production and the IM type where the columnar cells are replaced by mucin producing goblet cells similar to those found in the colonic mucosa.[2] The exact incidence of the two subtypes of CCG is uncertain; however, the IM type is less commonly reported[12] as was seen in our study (18.75% vs. 81.25%). In general, these changes are microscopic and detected as an autopsy finding in up to 60%–70% of the cases,[2,3] however, when the changes are florid, polypoidal masses can be seen in the urinary bladder which may cause clinical symptoms besides mimicking urothelial neoplasia.

The exact etiopathogenesis of CCG remains unclear, however, a chronic inflammatory condition has been implicated as its precursor. It has been associated with conditions such as recurrent urinary tract infections, prolonged catheterization, chronic bladder outlet obstruction, and pelvic lipomatosis.[4,13] However, in our study, we did not find such an association.

Although all the patients in our study were male, predilection for a particular sex in the development of CCG has not been demonstrated.[14] Similarly, all our patients were adults, with age ranging from 24 to 48 years, but the children can also be affected.[15]

The patients with CCG most commonly present with either irritative lower urinary tract symptoms, i.e., dysuria, frequency or with hematuria. Rarely, it can be an incidental finding on ultrasound examination carried out for some other indication. All the patients in our study were symptomatic with one or more symptoms and were diagnosed on transurethral biopsies. In our series, hematuria was the most common presenting symptoms (59.38%) followed by increased frequency of micturition (51.56%) and dysuria (48.44%). Eight patients had hydroureteronephrosis at presentation which resolved on the further follow up. One patient, in whom the lesions increased in extent, developed hydroureteronephrosis on the right side later during the follow-up, and continued to demonstrate it till the end of the study. However, he was asymptomatic with normal renal function and no specific intervention was performed.

The treatment of CCG includes transurethral resection and elimination of obstruction or chronic infection.[16] However, recurrence with resection alone may be common[17] and various modalities have been described in the literature to deal with the persistent disease: Intravesical Bacillus Calmette–Guérin;[18] intravesical chemotherapeutic agents;[19] oral steroids;[20] intravesical steroids;[21] laser ablation,[22] etc. However, optimal dosing schedule is not available for any of them. In our study we used transurethral resection as the sole modality of treatment and noted that the lesions completely resolved in 15 (23.43%) patients. In a series of 166 patients (155 in the typical group and 11 in the IM group), Yi *et al.* documented a resolution of the lesions only in the IM subgroup[23] and reported a complete resolution in 72% (8 out of 11 patients of IM type) of the patients. In our study, we noted a regression/resolution in 10 of the 12 (83.33%) patients with the IM type of CCG, which is comparable to findings of Yi *et al.* The lesions recurred in all the other patients, however, they were smaller in size in than the initial lesion in 34 patients and almost of the same size in 11 patients. Four patients had an increase in size of the lesions and all of them had IM type on histopathology. Hu *et al.* have developed a nomogram to predict the risk of recurrence in patients with CCG and found that besides urinary infections, long-term indwelling catheter and urinary calculus, squamous metaplasia and atypical hyperplasia were independent risk factors for CCG recurrence.[24]

Morgagni and Alexander described CCG for the first time in 1761, but the natural history of this entity remained elusive for a very long time.[25] The interest got renewed, when in 1950, an association between CCG and bladder carcinoma was first postulated by Immergut and Cottler.[6] Eight years later, in 1958, Shaw *et al.* also described a gradual transition of CCG to adenocarcinoma.[26] Thereafter, a number of more

reports were published implicating CCG as a premalignant condition, with ultimate progression to adenocarcinoma of the urinary balder.[8,9,27,28] Bullock, in 1987, reported his series of 11 cases with the IM type of CCG and found that 3 of these developed adenocarcinoma when followed up for more than 2 years.[7] Since then a number of studies have supported the association of CCG in general, and the IM histological variant of CCG in particular, with adenocarcinoma of urinary bladder.[29-31] Bryan *et al*. reported the production of β-catenin at the nuclear level in the IM type of CCG, rather than the membrane level in Typical type of CCG, making it more prone to development of malignancy.[32] This nuclear localization of β-catenin is also found in Barrett's esophagus, which is a preneoplastic condition for esophageal carcinoma.[33] Morton *et al*. demonstrated a significant telomere shortening in the IM type of CCG, besides the presence of similar chromosomal abnormalities as seen in the urothelial carcinoma thereby proving the association at a chromosomal level.[34]

In our series of 64 patients with a median follow-up of 5 years and 5 months, we did not have even a single case of progression to malignancy. The two subtypes of CCG were found to be comparable as far as the age at presentation, presenting symptoms, and resolution of the symptoms and lesions were concerned, however, more extensive lesions were detected in the IM group as compared to the typical group ($P = 0.0089$).

Our findings are also substantiated by others, who have considered CCG to be a benign histological lesion without any clinical significance except for the fact that they can mimic adenocarcinoma both during cystoscopy and on histopathology.[5,10,13] Corica *et al*. followed up 53 patients of IM type CCG for more than 10 years and showed that none of them developed bladder cancer.[35] This was also substantiated by Smith *et al*. in their study of 103 patients[11] and Yi *et al*. in their series of 166 patients with a median follow-up of 2.67 years.[23]

The retrospective analysis rather than a prospective study may be a shortcoming but gave us an advantage of thoroughly scrutinizing the records and to do a thread bare analysis. The long follow-up period of the study is a strength which would help adding to the existing data on the subject. However, the study is inherently limited by its inability to throw light on the etiopathogenesis and to make any therapeutic recommendations.

CONCLUSIONS

We did not find any increases in the risk of malignancy among patients with CCG (including the IM-type).

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