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Original Research Article

Correlation of morphological changes with demographical and clinicopathological parameters in cholecytectomy specimen

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Abstract

Background: Gall bladder carcinoma is the most common gastrointestinal cancer in Indian having poor prognosis due to advanced stage at presentation. There is marked geographical variation in the prevalence of GB carcinoma worldwide .Among the developed countries it is more prevalent in South American and Eastern European countries. The highest incidence of gallbladder carcinoma is found along the Gangetic plains of India.
Aim and Objective: The present study aim to correlate morphological changes with clinicopathological parameters (age of patients, number of stones and gallbladder wall thickness) and demographic parameters.
Materials and Methods: In our study 1500 cases of cholecystectomy specimens with stones were reviewed in span of 18 months. H and E sections were studied.
Result: 287/1500 cholecystectomy specimens precursor lesions were identified (122 hyperplasia, 135 metaplasia and 30 dysplasia).The age of the patients ranged between 18 years to 60 years. The wall thickness > 3 mm in 18%, 24% and 26% cases of hyperplasia, metaplasia and dysplasia respectively. The gallbladder specimens from all 287 patients with hyperplasia, metaplasia and dysplasia had either single or multiple stones. Multiple stones were found in 85%, 80% and 80% cases of hyperplasia, metaplasia and dysplasia respectively. Three types of stones were found (pigmented, cholesterol and mixed stones).
Conclusion: On comparing the GB wall thickness, number and types of gall stones in various precursor lesions there was no significant correlation suggesting that these parameters have no role in GB carcinogenesis. However, the duration of stone might play an important role in GB carcinogenesis as suggested in earlier studies.

Keywords: Metaplasia, Dysplasia, Hyperplasia, Carcinoma.

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1. Introduction

Gallbladder carcinoma is the most common malignancy of biliary tract.[1] It ranks 6th in frequency amongst the diagnosed malignancies of gastrointestinal tract.[2-5] The overall incidence of gallbladder carcinoma worldwide is 178,100 cases per year. There is marked geographical variation in the prevalence of GB carcinoma worldwide showing higher prevalence in developing countries as compared to developed part of world.[3] Among the developed countries it is more prevalent in South American and Eastern European countries.

In India it is one of the most common gastrointestinal cancer with prevalence rate 21.5/100000.[4] The highest incidence of gallbladder carcinoma is found along the Gangetic plains of India. It ranks sixth in Delhi amongst all cancers. It occurs more commonly in females as compared to males with male to female ratio of 1:6.[5] The incidence of gallbladder carcinoma increases with age and majority of the patients present in 5th and 6th decade of life.[6]

Majority of gallbladder carcinoma cases are diagnosed as an incidental finding in cholecystectomy specimens of patients operated for gall stones. Gallbladder carcinomas usually present at an advanced stage leading to difficulty in their management. The prognosis of gallbladder carcinoma is poor with a median survival of <6 months and overall 5 yrs survival of <5%.[7]

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The knowledge of risk factors of gallbladder carcinoma along with its pre-malignant lesions may help in early recognition of patients who are at high risk of developing carcinoma.

The two pathways proposed for gallbladder carcinogenesis:

1. Dysplasia-carcinoma pathway,[8]
2. Adenoma-carcinoma pathway.[9]

The precise genetic changes involved in the development of Gallbladder carcinoma are poorly understood. However, it has been proposed that alteration in normal cell cycle (G1-S) pathway and activation of proto-oncogens to oncogenes may have role in the development of carcinoma.

The pathogenesis for GB carcinoma is multifactorial with no single causative factor identified, the various risk factors proposed are:-

1. Demographic factors,
2. Gallbladder abnormality,
3. Exposure to carcinogens,
4. Specific Infection/ Infestation

2. Material and Methods

2.1. Study setting

Department of Pathology and Department of Surgery of tertiary care Hospital.

2.2. Study duration

November 2018 to September 2020

2.3. Study design

Analytical and cross sectional.

2.4. Sample size

Two year retrospective cholecystectomy specimens with gallstones. Sample size was calculated taking 50% as the maximum positivity with same precision.

The patient information, clinical details and all relevant data of the patients was taken from histopathological requisition forms and the confidentiality of the patients was maintained. Formalin fixed paraffin embedded blocks were retrieved from archives. All cholestectomy samples were evaluated for type of stone, and wall thickness, the histological findings (hyperplasia, metaplasia, dysplasia and carcinoma-in-situ).

2.5. Study population

Patients who had undergone cholecystectomy surgery at tertiary care hospital of Varanasi.

2.6. Inclusion criteria

All patients operated for gallstones and specimen received in Department of Pathology at tertiary care Hospital were included in the study.

2.7. Exclusion criteria

Histologically diagnosed cases of invasive gallbladder carcinoma.

2.8. Statistical analysis

Data obtained were used for descriptive statistics. Data was expressed as percentage/proportion and was depicted in the form of bar graphs, pie-charts and histograms to obtain descriptive statistics.

3. Results

Out of 1500 cholecytectomy specimen reviewed 1213 did not show any significant epithelial changes in the form of hyperplasia, metaplasia and dysplasia and had either normal flattened or ulcerated gallbladder mucosa. Xanthogranulomatous cholecystitis was present in 49 cases. Of 1500 cholecystectomy specimens 287 had epithelial changes, of which 122 had hyperplasia, 135 had metaplasia, and 30 showed features of dysplasia. The remaining 1330 cases had no signifiacnt epithelial changes in hyperplasia, metaplasia or dysplasia. **Table 1** shows the distribution of theses 287cases across various histological categories.

Two types of hyperplasia were identified a) papillary in which prominent folds of normal looking epithelium were present leading to mucosal crowding, b) Adenomatous also known as adenomyomatous hyperplasia in which increased proliferation of mucosa and inward invagination of Rokitansky aschoff sinus with glandular proliferation was found without muscular hypertrophy.

Two types of metaplasia were seen a) pyloric type metaplasia had glands which resembled gastric pyloric gland cells having abundant pale, apical mucin with nuclei at base, b) intestinal type had goblet cells which were columnar cell with mucin filled in it. (**Figure 2**)

Table 1: Distribution of 287 cases with epithelial changes across various histological categories

No. of Hyperplasia (122)		**No. of Metaplasia (135)**		**No. of Dysplasia (30)**	
Papillary	Adenomatous	Pyloric	Intestinal	Low grade	High grade
119	3	107	28	28	2

The cases with dysplasia were further categorized into low grade and high grade. In low grade dysplasia: there was stratification and overlapping of nuclei which were slightly enlarged plump and hyperchromatic nuclei with normal adjacent stroma. High grade dysplasia: characterised by loss of cellular polarity, nuclear stratification, marked nuclear enlargement, pleomorphism, hyperchromasia and mitotic figure.

3.2. Age distribution

The age of patients showing hyperplasia ranged from 18 to 50 years with mean age being 30 years.

The age of patients with metaplasia ranged from 20 to 50 years with mean age being 35 years.

Thirty patients having dysplasia were in the age group of 21 to 60 years with mean age being 39years. (**Table 2**)

Table 2: Age distribution of cases across various histological subtypes

Age group	Hyperplasia	Metaplasia	Dysplasia
≤20yrs	2	1	0
21-30yrs	66	75	3
31-40yrs	52	56	21
>40yrs	2	3	6
Total	122	135	30

3.2.1. Gender

1. Among 122 cases of hyperplasia, there were 40 (33%) males and 82(67%) females.
2. Among 135 cases of metaplasia, there were 45 (33%) males and 90 (67%) females.
3. Among 30 cases of dysplasia, there were 8(20%) males and 22(74%) females.

Table 3: Gender wise distribution of cases across various histological categories

Sex	No. of Hyperplasia (122)*	No. of Metaplasia (135)*	No. of Dysplasia (30)*
Male	40 (33%)	45 (33%)	8 (26%)
Female	82 (67%)	90 (67%)	22 (74%)

* Indicates total no. of cases in each histological categories.

3.3. Gallbladder wall thickness

The thickness of gallbladder wall was > 3 mm in 18%, 24% and 26% cases of hyperplasia, metaplasia and dysplasia respectively.

No statistically significant difference was found between the gallbladder wall thickness across various histological categories with p value >0.372.

Table 4: The gallbladder wall thickness across various histological categories

Gallbladder Wall thickness	No. of Hyperplasia (122)*	No. of Metaplasia (135)*	No. of Dysplasia (30)*
<3mm	100 (82%)	102 (76%)	22 (74%)
>3mm	22 (18%)	33 (24%)	8 (26%)

* Indicates no. of cases in various histological categories

3.4. Number of gallbladder stones

The gallbladder specimens from all 287 patients with hyperplasia, metaplasia and dysplasia had either single or multiple stones. Multiple stones were found in 85%, 80% and 80% cases of hyperplasia, metaplasia and dysplasia respectively.

Table 5: Number of gallbladder stones across various histological categories

No. of stones	No. of Hyperplasia (122)*	No. of Metaplasia (135)*	No. of Dysplasia (30)*
Single	18 (15%)	27 (20%)	6 (20%)
Multiple	104 (85%)	108 (80%)	24 (80%)

*Indicates no. of cases in various histological categories

No statistically significant difference was found between the number of stones across varies histological categories with p value >0.456.

3.5. Type of gallbladder stones

Three types of stones were found in cholecystectomy specimens based on colour, size and shape. These were pigmented, cholesterol and mixed stones.

Table 6: Types of gallbladder stones in various histological categories

Type of stone ↓	Hyperplasia*	Metaplsaia*	Dysplasia*
Pigmented	28 (22%)	29 (21%)	9 (30%)
Cholesterol	6(5%)	7 (5%)	3 (10%)
Mixed	88 (72%)	99 (73%)	18 (60%)
Total	122	135	30

*Indicates no. of cases in various histological categories.

Pigmented stones were small in size had irregular shiny surface and were either black or brown in colour. These stones were soft with rough flaky appearance. Majority of the pigmented stones found were brown.

Cholesterol stones were round to ovoid, and yellow white in colour. Outer surface was smooth with crystalline or laminated cut surface.(**Figure 3**)

Mixed stones were small mulitfaceted and grey white to black in colour and had dark core on cut surface.(**Figure 4**)

Of 122 cases of hyperplasia, 28 (22%) had pigmented stones, 6 (5%) had cholesterol and 88 (72%) had mixed stones.

Of 135 cases of metaplasia, 29 (21%) had pigmented stones, 7 (5%) had cholesterol and 99 (73%) had mixed stones.

Of 30 cases of dysplasia, 9(30%) had pigmented stones, 3 (10%) had cholesterol and 18 (60%) had mixed stones.

No statistically significant difference was found between types of gallbladder stones across varies histological categories with p value >0.556.

Figure 1: Picture of brown pigmented stones

Figure 2: Picture of black pigmented stones

Figure 3: Picture of cholesterol stone

Figure 4: Picture of mixed stone

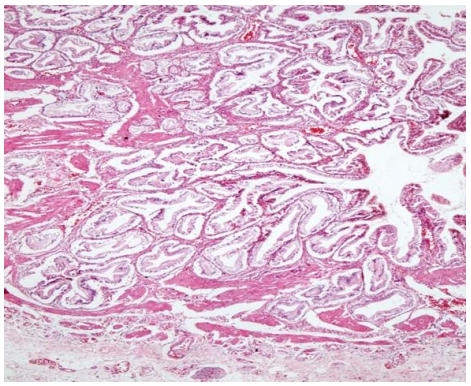

Figure 5: Picture of hyperplasia

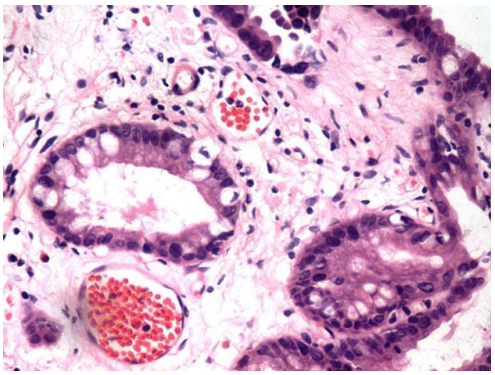

Figure 6: Picture of metaplasia

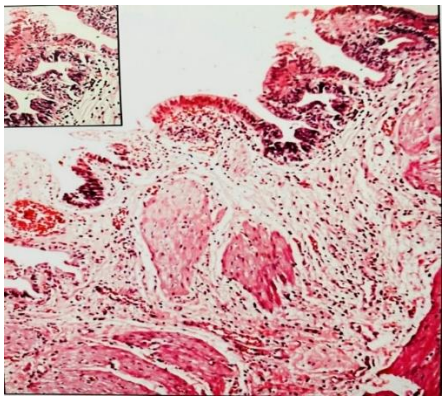

Figure 7: Picture of dysplasia

4. Discussion

Gallbladder carcinoma is one of the most malignant cancer of GI tract.[5,11] Two pathways of its carcinogenesis have been proposed: a) Dysplasia-carcinoma pathway,[8,12] b) Adenoma-carcinoma pathway.[9,13]

The exact pathway and relative importance of these pathways in GB carcinogensis is not clear. Hence the precursor lesions are not yet established.[14] Recently molecular work up has been done to find the specific mutations involved in GB carcinoma, and Garcia et al has proposed that mutation of some genes play important role in GB carcinoma.

There are few studies in the literature that have investigated the precursor lesions and in most of these studies only one or two immunological markers have been studied in the precursor lesions.

In our study 1500 cases of cholecystecomy specimens with stones were reviewed and out of these 1213 had no precursor lesions and revealed histopathological features of chronic cholecystitis, and xanthogranulomatous cholecystitis was present in 49 of them. The epithelial changes were found in 287 cases and showed features of hyperplasia, metaplasia and dysplasia in 122 (8%), 135 (9%) and 25(2%) cases respectively. In dysplasia cases adjacent epithelium had associated hyperplasia and intestinal metaplasia in 11 and 18 cases respectively. GB Dysplasia is an uncommon lesion as its prevalence is <3% in cholecystectomy specimens. Most of the dysplastic lesions present as a small focus adjacent to invasive GB adenocarcinoma. However, our study didn't include invasive carcinoma.[15] We found that majority 18/30 (60%) of dysplasia cases were associated with intestinal metaplasia, suggesting that metaplasia may be the precursor for dysplasia which may later progress to carcinoma.[16] In the many studies where 900 cholecystectomy specimens they found 34(3.7%) cases of dysplsia and 11 of those were associated with intestinal metaplasia, studied on 400 cholecystectomy specimen and found hyperplsia, metaplsia and dysplasia in 126 (31%), 95 (23%), 7 (1.75%) cases respectively. While hyperplasia, metaplasia and dysplsia in 62 (4.9%), 124 (9.8%), 19 (1.5%) cases respectively in the study which included 1259 cases of cholecystectomy specimens with stones. In our study the occurrence of precursor lesions is similar to above studies had also taken large sample size. But the prevalence of precursor lesion in our study was not in concordance with various other studies, the possible explanation for difference in prevalence of hyperplasia, metaplasia, dysplasia could be difference in sample size, selection criteria, criteria used for diagnosis of precursor lesions and population geographical variation.[17,18]

The ages of patients in our study ages of the patients ranged from 18 years to 60 years, which is similar to that found in other studies. However the mean ages of hyperplasia, metaplasia and dysplasia in our study was 30, 35 and 39 years respectively. The mean age of dysplasia was 47 years in the study conducted in other study. The mean ages of hyperplasia, metaplasia and dysplasia in the study done were 42, 42 and 56yrs respectively which is much higher than our study. Thus in our study the mean ages of various histological categories were lower compared to the previous studies. The possible explanation for this could be that we noted down the ages from the histological requisition form and which might not be accurate and correct ages of the patients. The higher mean age of presentation of dysplasia can be attributed to the time duration taken for development of dysplasia from chronic cholecystitis.

In our study all three types of lesions showed higher incidence in female with male to female ratio being 1:3 which is similar to the finding of various other studies. The higher prevalence in females can be atribuated to female hormones like estrogen, which leads to cholesterol supersaturation resulting in formation of stones and progesterone which retards gallbladder emptying leading to prolong staying of mutagens and resulting in carcenogenesis.

Of the 287 cases with precursor lesions in our study, the gallbladder wall thickness >3mm was found in 63 (21%) which was not statistically significant p value 0.467. In other studies found thickened wall (>3mm) in 60 of 140 (42%) cholecystectomy specimens. Multiple gall stones were found in 236 (82%) out of 280, and was not significant p value >0.05. Similar findings were also reported in earlier studies. Thus it seems that the number of stones and thickness of gallbladder wall has no effect on the development of precursor lesions.[18] However the duration of stone might have effect on the epithelial changes as the presence of the stones for longer duration will causes prolonged irritation of epithelium, leading to triggering of carcinogenesis pathway.[8,11,19]

In our study we found three kind of stones on the basis of colour, size and shape of stones: pigmented, cholesterol and mixed stones. Majority of the cases had mixed stones (70%) followed by pigmented stones (22%) and cholesterol stone (6%). Most of the pigmented stones were brown. However the difference in the type of stones was not significant among the various precursor lesions. According to other studies mixed stones were found in majority of cases followed by pigmented stone which was similar to our study, some studies found majority cases of pigmented stones (72%) followed by cholesterol stones (23%) and mixed stones (4.3%). In Indian population overall higher incidence of mixed and pigmented stones is due to various environmental factors like dietary habit, exposure to infection and obesity.[20,21]

5. Conclusion

The epithelial changes consisting of hyperplasia, metaplasia and dysplasia/ carcinoma-in situ were seen in 19% of total cholecystectomy specimens included in the study. The cholecystectomy specimens with epithelial changes included

122 (8%) cases of hyperplasia, 135 (9%) cases of metaplasia and 30 (2%) cases of dysplasia. Among hyperplasia cases 119 were of papillary hyperplasia and 3 of adenomatous hyperplasia; metaplasia cases included 107 pyloric metaplasia and 28 intestinal metaplasia and dysplasia cases revealed low grade dysplasia in 28 cases while high grade dysplasia/ carcinoma-in situ in 2 cases. Many dysplasia cases also had associated hyperplasia and intestinal metaplasia suggesting that dysplasia might have originated from hyperplasia or metaplasia. Low grade dysplasia was often seen adjacent to high grade dysplasia and carcinoma-in situ. On comparing the GB wall thickness, number and types of gall stones in various precursor lesions there was no significant correlation suggesting that these parameters have no role in GB carcinogenesis. However, the duration of stone might play an important role in GB carcinogenesis as suggested in earlier studies.

6. Source of Funding

None.

7. Conflict of Interest

None.

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