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Pathology

GALL BLADDER METAPLASIA: ITS PREVALENCE AND CORRELATION WITH DYSPLASIA AND CARCINOMA

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ABSTRACT

Background: Gallstones are the most common biliary pathology. Gall bladder metaplasia has been cited as precursor lesion of dysplasia and therefore carcinoma. The aim of study was to assess the prevalence of gallbladder metaplasia due to underlying cholelithiasis and to establish its correlation with dysplasia and carcinoma.

Materials and methods: All the post cholecystectomy samples during 1 year period from October 2017 to September 2018 submitted for histopathology comprised the study material.

Results: Total 359 cases were included, of which metaplasia was seen 152(42.3%). Antral metaplasia is commonest 104 (29.0%) followed by combined metaplasia cases 34 (9.5%) and than intestinal only cases in 14(3.9%). Significant correlation was seen between intestinal metaplasia to antral metaplasia and dysplasia.

Conclusion: Very high prevalence of metaplasia was observed. Antral metaplasia was more frequent than combined metaplasia followed by intestinal alone. Intestinal metaplasia was statistically correlated to dysplasia.

KEYWORDS : Metaplasia, Cholelithiasis, Antral, Intestinal

Introduction

Gallstones are the most common biliary pathology making cholecystectomy the most common abdominal surgery throughout the world. Carcinoma of gall bladder ranked 5th in frequency among gastro-intestinal cancer in the world and often carry dismal prognosis secondary to its late detection. Other conditions said to be associated with an increased risk of gallbladder carcinoma are cholecystoenteric fistula, porcelain gallbladder, ulcerative colitis, adenomyomatosis, (1,2) polyposis coli,(3) Gardner syndrome,(4) and anomalous connection between the common bile duct and the pancreatic duct.(5,6,7) Many of the latter cases present at an advanced stage.(8) The most common clinical manifestations of gallbladder carcinoma are right upper quadrant abdominal pain and anorexia, and the most common abnormal laboratory finding is elevated alkaline phosphatase level.

Many studies showed preceding events of carcinoma as inflammation-metaplasia-dysplasia and ultimately succumb to carcinoma. A large number of researchers believe that lithiasis and chronic inflammatory process are closely linked with these changes (9-12). Mataplasia is generally transformation of one mature tissue to another mature tissue that are more able to tolerate the adverse conditions (13). The role of antral metaplasia in gallbladder is still controversial. Many researchers consider it a preneoplastic lesion preceding the emergence of dysplasia, and it is similar to the association between intestinal metaplasia and gastric cancer (13-16). Other authors believe the foci of antral metaplasia are a common finding associated with chronic cholecystitis (17). Although, the metaplastic tissue may be resistant to injury but in the continued presence of injurious stimuli, it is prone to undergo dysplasia and finally carcinoma.(18) Gall bladder is one of the organs where metaplasia is seen rather frequently particularly in association with gall stones.

The aim of present study was to assess the prevalence of gallbladder metaplasia in patients who underwent cholecystectomy due to underlying cholelithiasis and to establish its correlation with dysplasia and carcinoma.

Materials and methods

The present retrospective study was conducted on 432 cholecystectomy specimens submitted for histopathological examination in the Department of Pathology at Rama Medical College, Kanpur, India over a period of 1 year from October 2017 to September 2018. Samples were also collected and advanced test performed at Lalpathlabs, Kanpur. Immediately after cholecystectomy, each gallbladder was opened and emptied. The fixed tissue specimens were divided into three sections corresponding to neck, body and fundus region of the gallbladder. Each region was longitudinally cut in 4 mm wide section, embedded in paraffin, cut and stained with hematoxylin and eosin for histological analysis.

Careful assessment of metaplastic changes was made for gastric and intestinal metaplasia by their characteristic features. Clinical features were noted in each case including the presence or absence of stones. Sections were taken from any suspicious areas of mural thickening or mucosal ulceration. Small masses or polyps were also submitted for histological examination. When dysplasia was found additional multiple sections were taken for microscopic examination to rule out carcinoma.

Inclusion Criteria

All the post-cholecystectomy gallbladder samples

Exclusion Criteria

Post cholecystectomy gallbladder samples with following pathological report

- Mucocele
- Porcelain gall bladder
- Acute infection, Empyema
- Partly/completely autolyzed tissue
- Structurally abnormal tissue
- Gall bladder with congenital anomalies

Results

There were total of 359 cholecystectomy specimens were included with male to female ratio in our study was 1:4.28. Figure 1 show sex distribution among study population

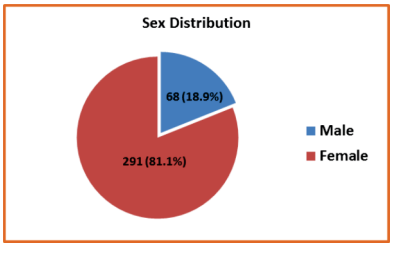


Figure1: Sex distribution among study population

Agewise, except for 8th and 9th decade, cases were nearly equally distributed. 3th& 4th decade accounted for approximately half of the

cases with age range from 7 to 78 years (mean age of 41.83) as shown in table 1.

Table 1: Distribution of cases according to age groups.

S.No.	Age Groups(in years)	No.of Cases	Percent (%)
1.	0-10	2	0.6
2.	11-20	4	1.1
3.	21-30	96	26.7
4.	31-40	91	25.3
5.	41-50	65	18.1
6.	51-60	65	18.1
7.	61-70	30	8.4
8.	71-80	6	1.7
TOTAL		359	100

On observation, Careful assessment of metaplastic changes was made like cells having abundant pale, apical mucin that compresses nuclei at the base seen in gastric metaplasia (Figure 2a&b) and mucin containing goblet cells feature present in intestinal metaplasia. (Figure 2c) Dysplasia was noted whenever these features were present in the form of loss of polarity, hyperchromasia, nucleomegaly, peudostratification and atypical mitosis (Figure 2d) Diagnosis of Adenocarcinoma was made when infiltrating glands were present along with dysplasia. (Figure2e)

Figure 2a: Antral metaplasia with chronic inflammatory infiltrate (H&E, 100x)

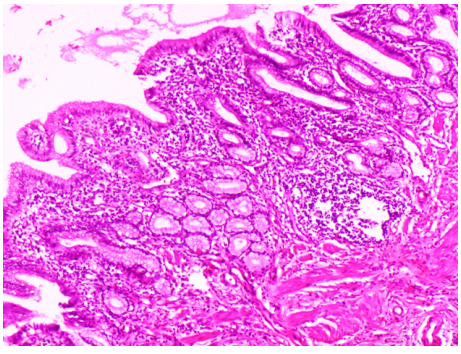


Figure 2b: Antral metaplasia with chronic inflammatory infiltrate (H&E, 400x)

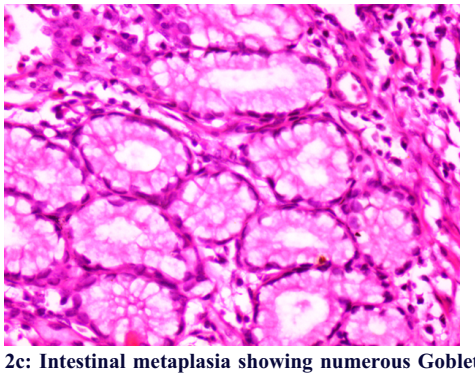


Figure 2c: Intestinal metaplasia showing numerous Goblet cells (H&E, 100x)

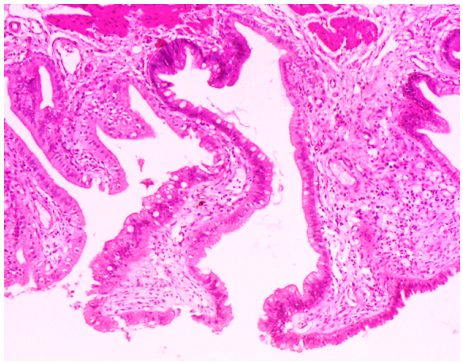


Figure 2d: Intestinal metaplasia associated with Dysplasia (H&E, 400x)

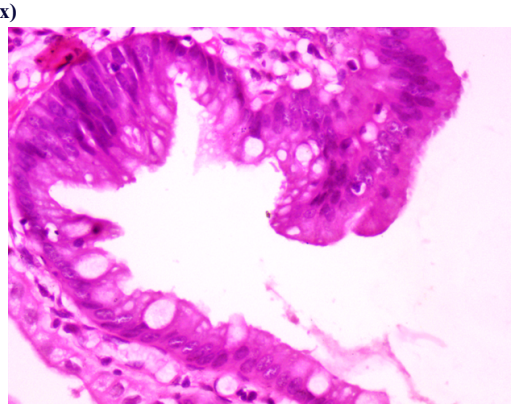
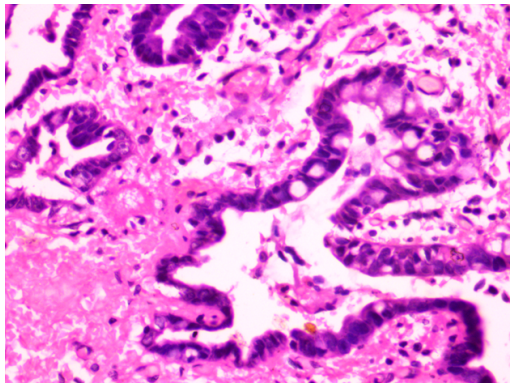


Figure 2e: Intestinal metaplasia associated with Adenocarcinoma (H&E, 400x)



All specimens examined were radiologically diagnosed as cholelithiasis and may presented as abdominal pain and flatulence. The breakup of final histopathological diagnosis with mean age is given in table 2:

Table 2: Distribution according to histological diagnosis with mean age

S.No	Diagnosis	Cases (n)	Percentage (%)	Mean age
1.	Chronic cholecystitis with no metaplasia	183	51.0	41.16
2.	Chronic cholecystitis with pyloric metaplasia	104	29.0	43.26
3.	Chronic cholecystitis with intestinal metaplasia	14	3.9	48.51
4.	Chronic cholecystitis with both pyloric and intestinal metaplasia	34	9.5	44.09
5.	Dysplasia	13	3.6	49.14
6.	Malignancy	11	3.0	49.31
7.	Total	359	100	42.87

This study showed predominance of female patients in all final histopathological diagnosis. No significant correlation is seen between metaplasia in different regions of gall bladder. All cases showed presence of stones in which 66 (18.4%) cases had single large stone and 293 (81.6%) cases had multiple small stone.

A statistically significant association was found between intestinal metaplasia and intestinal metaplasia (P = 0.005) as shown in table 3.

Table 3: Association of Antral-Type Metaplasia and Intestinal Metaplasia

Antral type Metaplasia	Intestinal Metaplasia		
	Absent	Present	Total
Absent	190	18	207
Present	110	41	151
Total	300	59	359

A statistically significant association was also found between intestinal metaplasia and dysplasia (P = 0.001) as shown in table 4, however

antral metaplasia was not significantly correlated with dysplasia

Table 4: Association of intestinal Metaplasia and dysplasia

Intestinal metaplasia	Dysplasia		
	Absent	Present	Total
Absent	295	3	298
Present	51	10	61
Total	346	13	359

A statistically significant association was found between dysplasia and carcinoma ($P < 0.002$) as shown in table 5.

Table 5: Association of dysplasia and carcinoma

Dysplasia	Carcinoma		
	Absent	Present	Total
Absent	335	8	343
Present	13	3	16
Total	348	11	359

Distribution of cases with type of metaplasia associated with advanced lesion was shown in table 6.

Table 6: Distribution according to metaplasia in advanced lesion

Diagnosis	Antral	Intestinal	Combined	None	Total
Dysplasia	4	2	4	3	13
Malignancy	3	2	3	3	11
Total	7	4	7	6	24

Discussion

Gall bladder carcinoma generally shows aggressive behavior and poor prognosis of the patient due to absence of specific biomarker and reliable screening tool. Oftenly it is discovered unexpectedly during histological examination of cholecystectomy specimen performed for chronic cholecystitis with cholelithiasis (19). The normal mucosa of gallbladder in fetus, children and adolescents do not show metaplasia(16).

Different studies cited in review of literature shared different results largely due to contribution of various factors like ethnic and geographical. There is dearth of Indian studies citing the relationship of cholecystitis to metaplasia to malignancy. Also quantitative or semi-quantitative data for grading of metaplasia and its extent is seriously lagging in studies across the globe.

In our study there were total of 359 cholecystectomy specimens included, out of which 68 were males and the 291 were females. The mean age at the time of operation was 41.83 years. The mean age in our study at the time of cholecystectomy is close to the figure by Tyagi et al (20) and Sharma et al (21). However, many studies showed slightly higher average age (22, 23, 24).

Female to male ratio in present study was 4.3:1. The figure was close to the study by Reinaldo et al (25) and lower than study of sharma et al (21), Tyagi et al (20) and Mohan et al (26). However, higher than study of Helmut et al (22) and Rizwam KM et al (24).

For convenience and prompt comparison with previous published data table 7 enumerate the results cited to compare with present study

Table 7: Comparison of various studies in prevalence of metaplasia

Studies	Cases	Metaplasia	Pyloric	Intestinal
Rizwam KM te al (24)	293	NA	NA	39
Sharma et al (21)	119	46.2	42.5	16
Seretis C et al (27)	86	25.6	9.3	1.2
Helmut et al (22)	1514	NA	22.8	2.2
Mukhopadhyay S et al (23)	400	NA	59.5	9.8
Reinaldo K S et al (25)	35	NA	60	NA
Yamagiwa et al (28)	1000	NA	NA	30.6
Duarte et al (13)	162	NA	95.1	58.1
Martinez- guzman et al (29)	1367	NA	50	16
Khanna et al (30)	140	NA	16.5	15.5
Stancu et al (31)	3901	5	NA	NA
Present study	359	42.3	38.4	13.4

Our study showed presence of metaplasia in 42.3% of cases, in which 38.4% showed antral metaplasia and 13.4% showed intestinal metaplasia, which was consonant to the study of Sharma et al (27) and Martinez-Guzman et al (29). Duarte et al showed highest incidence of 95.1% antral and 58.1% intestinal metaplasia.(13) and Stancu et al showed least incidence of metaplasia (31). Our study also showed 9.5% cases having both antral and intestinal metaplasia. Only antral metaplasia seen in 104(29.0%) cases, only intestinal metaplasia seen only 14 (3.9%) of the cases. However, Both antral and intestinal metaplasia was noted in 34 (9.5%) cases. Hence, it may be concluded that intestinal metaplasia tend to develop more in association with pyloric metaplasia as compared to only intestinal metaplasia. However incidence of pyloric metaplasia is not influenced by intestinal metaplasia.

Association between antral-type metaplasia and intestinal metaplasia found to be statistically significant (Table 3) and significant correlation was also noted between intestinal metaplasia and dysplasia (Table 4). In many cases, antral-type metaplasia was in continuation to intestinal metaplasia, and intestinal metaplasia to dysplasia. However, no statistically significant association was seen between antral-type metaplasia and dysplasia. This lag of association was contributed by histologic examination, in which most cases did not show any contiguity and antral-type metaplasia and dysplasia were the only changes seen. The distribution of the various metaplastic changes did not follow any pattern in terms of site of occurrence in the neck, body, or fundus of the gallbladder.

A significant correlation was present between dysplasia and carcinoma (three cases of adenocarcinoma with concomitant dysplasia) (table 5). This findings was in agreement to earlier studies.(13,27-30).

Present study showed 76.9% and 72.7% prevalence of metaplasia in dysplasia and adenocarcinoma respectively (table 6) further supporting occurance of metaplasia to dysplasia to malignancy sequence of chronic cholecystitis. Earlier studies also showed high degree metaplastic and dysplastic lesions were identified near the carcinoma territories in 73–92% of cases (9,32,33) supporting the findings of present study. The dysplastic modifications are almost always developed in the metaplastic mucosa, initially on the surface, then extending in the deep glands (28, 32, 33).

All cases showed presence of stones in which 66 (18.4%) cases had single large stone and 293 (81.6%) cases had multiple small stone. Miocrolithiasis was associated with 86.8% of metaplasia, is agreement of the findings of Seretis C et al (27) and Rizwam KM et al (24).

Our study also showed increase in mean age with the advancement of the lesion Despite this, the findings of other authors indicate that the progression from pyloric metaplasia to dysplasia takes approximately three years, and from dysplasia to carcinoma, fifteen years (34, 35). This finding was similar to those of this study in term of dysplasia, however showed disagreement in case of carcinoma.

Antral metaplasia could precede intestinal metaplasia, which could precede dysplasia following carcinoma. This sequence is supported by age difference which is smaller in antral metaplasia and it progressively increases in intestinal metaplasia and even more in dysplasia and malignancy (23).

This study mainly showed increased prevalence of epithelial metaplasia in gall bladder with chronic inflammation secondary to lithiasis, in agreement of previous literature across the different region of globe (13,28) further established two histogenic models of carcinogenesis: one arising from normal epithelium and other from metaplastic epithelium. Both models might have different biological behavior and prognosis. (16,28,36)

Conclusion

Very high prevalence of metaplasia in routine cholecystectomy specimen was observed. Antral metaplasia was the most frequent followed by combined antral and intestinal as compared to intestinal alone. Intestinal metaplasia showed statistical significant correlation with antral metaplasia and dysplasia. Dysplasia is also significantly correlated with carcinoma. Anatomical regions of gall bladder showed no relation with development of the metaplasia.

More exhaustive and elaborated study is required to understand natural history of metaplastic changes in gall bladder and to grade the metaplastic foci in absolute number for better communication to understand the risk of progression into advanced lesion and to be included in reporting format.

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