ORIGINAL ARTICLE

Gallbladder Mucosal Changes Associated with Chronic Cholecystitis and Their Relationship with Carcinoma Gallbladder

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Abstract

384 cholecystectomy specimens were examined during a period of one year from Oct 2005 to Oct 2006, in the department of Pathology, ASCOMS, Sidhra. Jammu, for studying the histological patterns of chronic cholecystitis, the frequency of associated mucosal changes, the age related incidence and the relationship of carcinoma with various mucosal changes. Majority of patients presented in the fourth decade of life. The youngest patient was 16 years and the oldest 78 years of age. Acute and chronic inflammatory lesions were associated with ulceration in 13.02%, mucosal hyperplasia in 25.26% and antral metaplasia in 53.40%. Intestinal metaplasia constituted 9.11%, cholesterolosis was seen in 12.25%, dysplasia in 3.64% and neoplasia in 0.78% of cases. All the cases of carcinoma were associated with gallstones. Histological continuity between epithelial changes was seen in 35 cases. 8 cases had continuity of antral metaplasia, intestinal metaplasia and dysplasia. 2 cases showed continuity of intestinal metaplasia with dysplasia and carcinoma and 1 case showed continuity of dysplasia with carcinoma.It is inferred that antral metaplasia, intestinal metaplasia, dysplasia and carcinoma have an inter-relationship. There is a significant higher incidence of carcinoma gallbladder in patients who harbor gallstones for longer period. Histopathological examination is thus important in every case of cholecystectomy for identifying metaplasia, dysplasia and carcinoma.

Key Words

Gallstones, Antral metaplasia, Intestinal Metaplasia, Dysplasia, Carcinoma Gallbladder

Introduction

Carcinoma of the gallbladder is the 5th commonest G I malignancy. It is two to four times more common in females than in males (1). The pathological changes related to gallstone formation are still the focus of intensive research. The hypothesis most widely accepted is the stasis of bile caused by gallbladder dyskinesia, while dyskinesia may be the result of pathologic changes in the gallbladder wall (2). Patients with gallstones need strict surveillance by imaging techniques. Gallstones mainly injure the mucosal columnar epithelium and thus cause changes like metaplasia, dysplasia and neoplasia (3). Mucosal dysplasia and carcinoma in situ are frequently found in mucosa close to invasive carcinoma. Some cases of atypical hyperplasia may progress to carcinoma in situ and a proportion of these to invasive carcinoma (4) .

Cholelithiasis is found in all cases of gallbladder carcinoma (5). Most of gallbladder carcinomas originate in fundus (60%), body (30%) and neck (10%). Grossly 10 to 37% of gallbladder carcinoma can not be identified with certainty (6). Highest frequency of carcinoma is found amongst females over 65 years of age (7).Metaplasia usually progresses to dysplasia and adenocarcinoma via a multistep process which may result from accumulation of genetic abnormalities (8).Prognosis of advanced gallbladder carcinoma is grave but histological presentation may uncover a group of patients with symptomatically better prognosis as carcinoma in situ and microinvasive carcinoma can be treated by cholecystectomy alone (9). Cholelithiasis and even silent gallstones which are asymptomatic produce a series of

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epithelial pathological changes in gallbladder mucosa, which could be precursor lesions of gallbladder carcinoma (10). The results of this study strongly suggest that cholelithiasis and cholecystitis produce a series of mucosal pathological changes, which represent precursor lesions of carcinoma gallbladder.

Mateial and Methods

The study was carried out on 384 cholecystectomy specimens that were sent to the department of Pathology ASCOMS, for histological examination over a period of one year . Detailed history, clinical findings, investigations, operative procedure along with gross examination of gallbladder was done. The tissue was fixed in 10% buffered formal saline, processed routinely and embedded in paraffin. Sections were stained with H&E. Special staining was done wherever required.

A detailed histopathological examination with respect to epithelial changes, formation of Aschoff-Rokitansky sinuses, inflammatory cell infilterate, metaplasia and neoplastic changes was carried out.

Results

Majority of patients were females (279) accounting for 72.66%, whereas males were only 105, constituting 27.34%. Female to male ratio was 3:1. 52% of the cases (196) were between 31-50 years of age. Out of 384 cases, 62 (16.15%) were obese and 29 (7.55%) cases were rather thin and rest 293 (76.30%) were within normal weight range. The weight of the patients ranged from 38-113 kg. On USG cholelithiasis was the commonest finding in 380 cases accounting for 98.95% of patients. A GB mass could be detected in only 1 patient on USG.

Majority (191) of cholecystectomy specimen were less than 7 cm in length accounting for 49.75%, followed by 140 cases(36.46%)between 7-10cm in length and 38 (9.89%) cases larger than 10 cm. Majority of the cases (288) had chronic cholecystitis (75%). 8 cases had follicular cholecystitis (2.08%), xanthogranulomatous cholecystitis was seen in 4 cases(1.04%), empyema was present in 21 cases (5.47%) and acute on chronic cholecystitis was seen in 10 cases (2.60%). 47 cases had cholesterolosis (12.25%), and 3 cases (0.78%) were of neoplastic lesions.(*Table-1*) Ulceration of mucosa was seen in 50 cases (13.02%). Hyperplasia of mucosal folds was seen in 97 cases (25.02%). Proliferation of mucous glands (Antral metaplasia) was seen in 205 (53.40%) cases. Intestinal metaplasia was seen in 35 cases (9.11%). Haemorrhages were present in mucosa in 50 (13.02%) cases. R-A sinuses were present in 172 (44.80%) cases. Dysplasia was seen in 14 (3.64%) cases, and neoplasia was seen in 3 (0.78%) cases. (*Table-2*)

Out of 384 cases Antral metaplasia was present in 205 cases and intestinal metaplasia was present in 35 cases. In 27 cases both antral metaplasia and intestinal metaplasia were present, and this association was found to be statistically significant. ($p<0.01$, DF:1, x2 test.).(*Table-3*). Out of 35 cases of intestinal metaplasia, dysplasia was present in 14 cases and this association was found to be statistically significant. ($p<0.001$, DF: 1, x2 test). (*Table-4*).Histological continuity or blending was found between multiple epithelial changes in the same section in 35 cases. Of these 8 had continuity of AM, IM and dysplasia. 2 cases showed continuity of IM with dysplasia and carcinoma, and 1 case showed continuity of dysplasia with carcinoma. Out of 5 cases in which AM and dysplasia were seen in the same section, continuity was found only in 1 case, and in 19 cases in which AM and IM were seen in the same section, blending or histological continuity was seen in 12 cases and rest of the 7 cases showed no histological continuity.(*Table-5*).*Fig (1&2)*

Table1. Histopathological Diagnosis (N=384)

Histopathological Diagnosis	No. of Patient	% ag
Chronic Cholecystitis	288	75
Follicular Cholecystitis	8	2.08
Eosinophilic Cholecystitis	3	0.78
Xanthogranulomatous Cholecystitis	4	1.04
Empyema Gallbladder	21	5.47
Acute on Chronic Cholecystitis	10	2.60
Cholesterolosis	47	12.25
Neoplasia	3	0.78

Table 2. Microscopic Changes In Mucosa (N=384)

Microscopic Changes	Total	%Age
Ulceration of Mucosa	50	13.02
Hyperplasia of Mucosa	97	25.26
Antral Metaplasia	205	53.40
Intestinal Metaplasia	35	9.11
Rokitansky-Aschoff Sinuses	172	44.80
Mucosal Haemorrhages	50	13.02
Dysplasia	14	3.64
Malignancy	3	0.78

Table3. Association of Antral Metaplasia with Intestinal Metaplasia

Antral Metaplasia	Intestinal Metaplasia		
	Absent	Present	Total
Absent	171	8	179
Present	178	27	205
Total	349	35	384

Table4. Association of Intestinal Metaplasia and Dysplasia

Intestinal Metaplasia	Dysplasia		
	Absent	Present	Total
Absent	344	5	349
Present	26	9	35
Total	370	14	384

Fig.1.Intestinal and Antral Metaplasia Gallbladder (H&EX100)

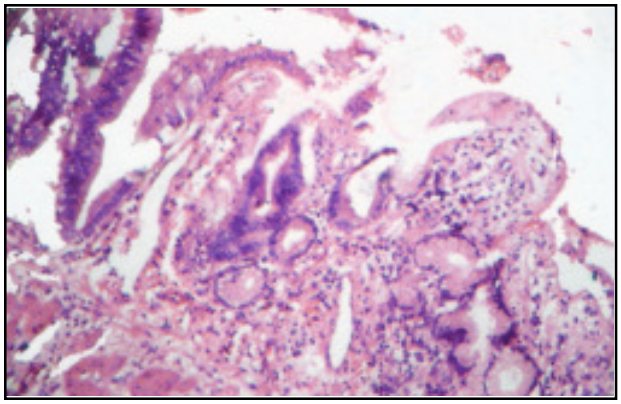
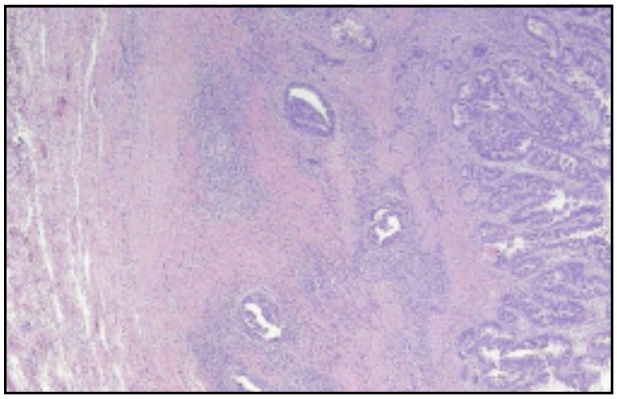


Table5. Histological Continuity Observed in Cases with Multiple Epithelial Changes in the Same Section

Epithelial changes observed	No. of Cases	Epithelial changes in direct continuity with each other	No. of cases
AM, IM. D.	8	AM with IM, IM with D and AM with D.	6
		IM with D only.	2
		IM with D & C	2
IM, D, C	3		
		D with C	1
		AM with D	1
AM, D	5	No continuity of changes	4
	19	AM with IM	12
AM, IM.		No continuity of changes	7

Note; AM: Antral metaplasia; IM: Intestinal metaplasia; D: Dysplasia ; and C: Carcinoma

Fig 2.Gallbladder Shaowing Hyperplastic Mucosa Revealing Dysplastic Changes (H&E X 50)



Discussion

The results of our study strongly suggest that cholelithiasis and cholecystitis produce a series of mucosal pathological changes which represent the precursor lesions of carcinoma. The findings suggest that antral metaplasia and intestinal metaplasia are precursors of dysplasia in gallbladder. This is consistent with the findings of Mukhopadhyay S, *et al*,(11), who suggested that dysplasia arises from a precursor lesion and not directly an inflammatory background. In our study 76.3% (293) cases were within normal weight range. This was in sharp contrast to the concept given by Csendes A, *et al* (12), Maclure KM *et al* (13), and Scragg RK, *et al* (14), that obesity is an important risk for gallstone diseases. The frequency of carcinoma in this study was 0.78% (3 out of 384 cases), which is consonant with gallbladder cancer rate reported by Bani-Hani KE *et al*, (15), as 0.73%, Gurlayck G *et al*, (16), as 1%. Mohan H *et al*,(17), as 1.09% and Zahrani IH *et al*,(18) as 1%. All 3 cancers were well differentiated adenocarcinomas. Metaplastic epithelium is more susceptible to malignant transformation rather than normal one (19). Our findings strongly suggest that the usual sequence for development of invasive carcinoma is conversion of dysplasia to carcinoma in situ.(19, 20, 21). In the gallbladder, the epithelial changes cannot be recognized grossly with certainty. Discrepancies between findings of different authors in frequency and distribution of epithelial changes may be explained by sampling and technical errors.

The focal and/or patchy distribution of mucosal changes in gallbladder should be taken into account in studies designed to determine their actual incidence as limited number of histological samples usually taken in routine examination seem to be insufficient to detect all

cases with dysplasia and/or carcinoma in situ, as may be inferred from randomly selected sections (22).

Conclusion

It is inferred that antral metaplasia, intestinal metaplasia, dysplasia and carcinoma have an inter-relationship. There is a significant higher incidence of carcinoma gallbladder in patients who harbor gallstones for longer period. Histopathological examination is thus important in every case of cholecystectomy for identifying metaplasia, dysplasia and carcinoma.

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