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Patterns of mucosal alterations in gallbladder disease with special reference to metaplastic changes: a ten year experience in a tertiary teaching hospital in Western Uttar Pradesh, India

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Abstract:
Background: *Gallbladder disease shows a variable spectrum of pathological conditions. Gallstone disease is the most common disorder leading to continuous chronic irritation to gallbladder mucosa. A variety of non-neoplastic, dysplastic and malignant changes may develop.* ***Aims:*** *The present study was done to evaluate mucosal alterations in gallbladder diseases.* ***Settings and design:*** *Hospital based and retro-prospective study.* ***Results:*** *A total of 2458 resected gallbladder specimens were studied in this study. Cholelithiasis was seen in 2194 cases. Non-neoplastic, premalignant and malignant lesions were studied. Most common type of epithelial change encountered was metaplasia, followed by hyperplasia.* ***Conclusions:*** *Chronic chlolecystolithiasis is the main culprit for epithelial alterations in gallbladder. Timely surgical resection of symptomatic gallstone disease is the standard strategy.*

Keywords: *Carcinoma, Cholelithiasis, Dysplasia, Gallbladder, Metaplasia.*

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I. Introduction

The gallbladder falls in the group of the most commonly surgically removed organs. The number of gallbladder resections is showing an increasing trend worldwide.[1, 2]

Gallbladder disease exhibits a vast spectrum of pathological conditions ranging from congenital anomalies, inflammatory pathology, and non-invasive neoplastic lesions to frank invasive malignancies. Gallstone disease is the most common disorder of gallbladder affecting nearly 10-20 % of adult population in developed countries.[3]

Initially, there is 'biliary sludge' formation containing mucous gel, hydrophobic bile pigments, cholesterol lecithin liquid crystals, and solid cholesterol monohydrate crystals. Later, crystal nucleation seems to be occurring in the mucous gel on the mucosal surface. Thus, the sequence of cholelithiasis is: bile super saturation →nucleation → precipitation of crystal → formation of stone like aggregates.[4]

Gallstone disease leads to chronic mucosal irritation. Mucosa of the chronically inflamed gallbladder depicts mononuclear infiltrate and fibrosis of variable magnitude. The epithelium may be relatively normal or may exhibit atrophic or hyperplastic and metaplastic alterations.[5]

The metaplasia can be of goblet cells (intestinal) or pseudo pyloric (antral) type. Metaplastic glands, in contrast to normal glands, contain nonsulfated acid mucin and neutral mucin but little sulfated mucin.[6, 7]

The incidence of metaplastic changes show a rising trend with age.[8]

The present study was designed to evaluate the patterns of mucosal alterations in gallbladder diseases with special reference to hyperplastic and metaplastic changes in our institute.

II. Material And Methods

The present study was a ten years hospital based retro-prospective type of study (08 years retrospective and 02 years prospective study) from April 2009-March 2019, conducted on cholecystectomy specimens received in the Department of Pathology in a tertiary teaching hospital in Western Uttar Pradesh, India. Approval of the institutional ethical committee was taken. All the relevant data, paraffin embedded tissue blocks and histopathology slides of gallbladder disease available in the archives of Department of Pathology were thoroughly studied.

Sample size: A total of 2458 cholecystectomy specimens were included in the study.

Inclusion criteria: All the cholecystectomy samples falling during the specified period of time submitted for histopathological examination in the histopathology department.
Exclusion criteria: Autolysed samples, samples with poor preservation effects visualized on microscopy, acute cholecystitis cases.
Statistical analysis
Chi-square test was applied as per requirement and feasibility.

III. Result

In the present study we studied 2458 cholecystectomy specimens which were received in the Department of Pathology. Majority of cases were of female patients, i.e.2005 cases (81.57%), while 453 cases (18.43%) belonged to male patients. Male: Female ratio came out to be 1:4.4.

Maximum patients belong to fifth decade of life, followed by fourth decade. Cases were distributed from 14 years of age to 88 years of age. Mean age in gallbladder pathology was 51 years.

Patients below third decade of life usually had classical chronic cholecystitis features with chronic inflammation or with simple epithelial invaginations. Advanced epithelial alterations started from the fourth decade of life and showed an increasing trend with age.

Stones were present in 2194 cases (89.26%). Multiple stones were present in 1832 cases while 362 cases had single stone.

In specimens with more than one mucosal response, the more advanced pattern was taken into account. Classical chronic cholecystitis cases with near normal mucosa or with simple epithelial invaginations (Rokitansky Ashoff sinuses) were taken as chronic cholecystitis with classical features. But if they also had metaplasia, or hyperplasia, atrophy or dysplasia they were categorized as per the advanced mucosal alteration.

Most common epithelial change seen was metaplastic changes followed by hyperplastic changes. Cholecystitis with hyperplasia included stratification and adenomyomatous changes.(Table 1)

TABLE 1: Patterns of epithelial changes in gallbladder lesions in correlation to presence or absence of gallstones

DISTRIBUTION OF CASES	WITH STONES	WITHOUT STONES
Cholecystitis with classical features -without hyperplastic/ metaplastic or dysplastic changes (n=1132)	950	182
Cholecystitis with hyperplasia (n=150)	135	15
Cholecystitis with metaplasia (n=1043)	1005	38
Cholecystitis with low grade dysplasia (n=62)	54	08
Cholecystitis with high grade dysplasia/ carcinoma in situ (n=26)	20	06
Carcinoma gallbladder (n=45)	30	15
TOTAL (n=2458)	**2194 (89.26%)**	**264 (10.74%)**

Correlation of gallbladder conditions in association with gallstones was found to be statistically highly significant. ($p < 0.0001$).

TABLE 2: Patterns of epithelial changes in gallbladder lesions in correlation to number of gallstones

Mucosal alterations due to gallstones	Number of stones	
	Solitary stone	**Multiple stones**
Cholecystitis with classical features (without hyperplastic/ metaplastic or dysplastic changes) (n=950)	187 (19.68)	763 (80.32%)
Cholecystitis with hyperplasia (n=135)	29 (21.48%)	106 (78.52%)
Cholecystitis with metaplasia (n=1005)	140 (13.93%)	865 (86.07%)
Cholecystitis with low grade dysplasia (n=54)	04 (07.41%)	50 (92.59%)
Cholecystitis with high grade dysplasia/ carcinoma in situ (n=20)	00 (0.00%)	20 (100%)
Carcinoma gallbladder (n=30)	02 (6.67%)	28 (93.33%)
TOTAL (n=2194)	362 (16.45%)	1832 (83.55%)

Statistical correlation between number of stones and pattern of epithelial alteration came out to be insignificant in the present study.

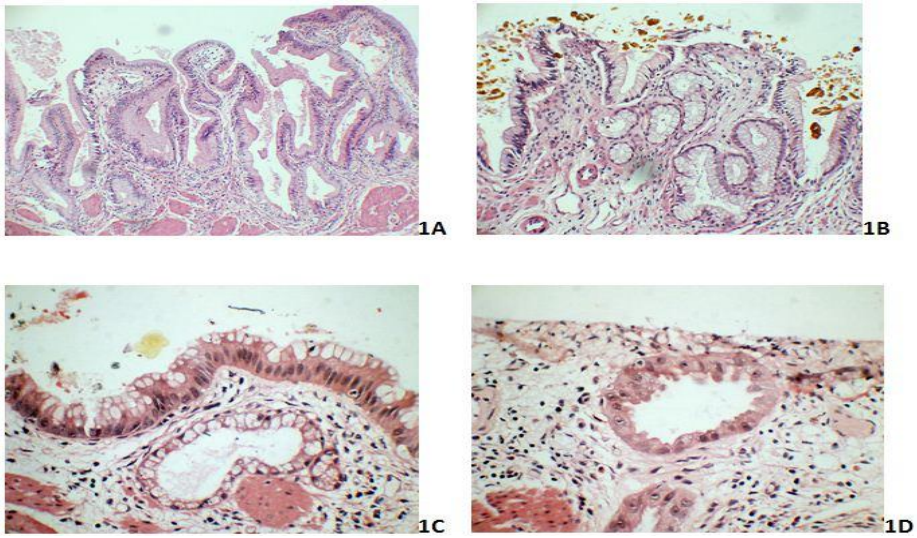
Metaplastic changes were observed in 1043 cases. (Image 1) Most common metaplastic change seen was pseudopyloric type followed by intestinal type, followed by squamous type. (Table 3)

TABLE 3: Patterns of metaplastic changes in non neoplastic epithelial alterations in gallbladder lesions

Metaplastic epithelial changes	**Number of cases**
Pseudopyloric metaplasia	923
Intestinal metaplasia	114
Squamous metaplasia	06
Total	1043

IMAGE 1

Mucosal alterations in gallbladder diseases

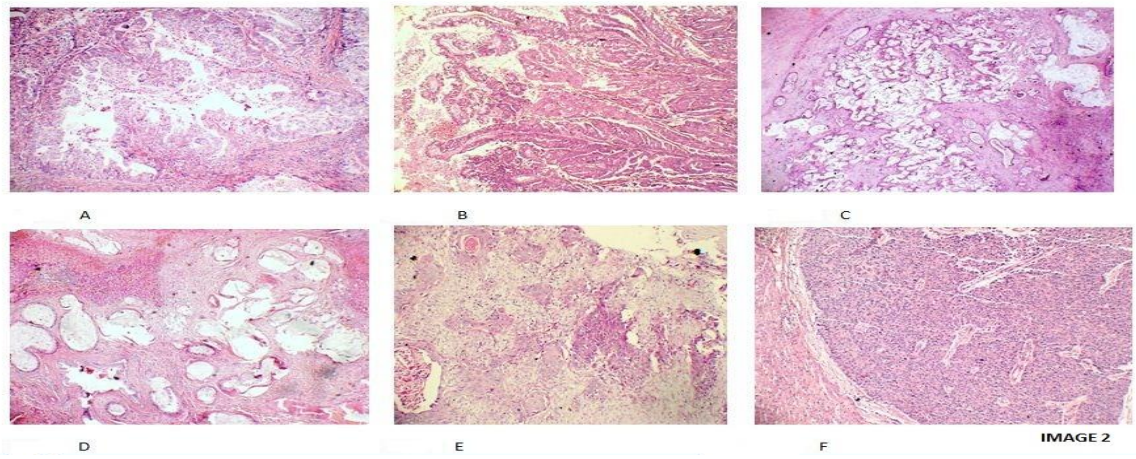


1A Hyperplastic epithelium (H&E X 200), **1B** Pseudopyloric metaplasia (H&E X 200), **1C** Intestinal metaplasia (H&E X 400), **1D** Pseudopyloric metaplasia with dysplastic changes (H&E X 400)

Malignant changes were seen in 45 cases. (Image 2)
Adenocarcinoma-conventional type was seen in 34 cases.
Papillary adenocarcinoma was seen in 03 cases,.
Two cases each of mucinous adenocarcinoma, adenosquamous and neuroendocrine carcinoma, followed by one case each of small cell and undifferentiated carcinoma were also encountered.

IMAGE 2-

Carcinoma gallbladder with various histological variants



A- Adenocarcinoma- conventional type (H&E X 100),B- Papillary adenocarcinoma (H&E X 100),C- Mucinous adenocarcinoma (H&E X 100),D-Mucionous adenocarcinoma metastatic to liver (H&E X 100),E-Adenosquamous cell carcinoma(H&E X 100),F-Neuroendocrine carcinoma(H&E X 100)

IV. Discussion

Gallbladder lesions show a clear cut female preponderance. In our study, Male: Female ratio came out to be 1:4.4. This is close to the findings of Sood et al[9] who observed M: F ratio to be 1:4.5 in their study.

Epithelial alterations are common in gallbladder pathology. Hyperplastic, metaplastic and dysplastic lesions are considered as potential precursors of gallbladder carcinoma.[10]

The most common cause of mucosal changes was chronic persistent irritation due to cholelithiasis. Serentis et al[11] found in their study that cholelithiasis and even microlithiasis appears to be more frequently associated with early metaplastic and dysplastic changes.

Non neoplastic mucosal alterations in gallbladder comprises of hyperplastic and metaplastic lesions.

In hyperplasia, there is increased proliferation of mucosa only without muscular hypertrophy while in adenomyomatosis, there is increased proliferation of the mucosa in addition to hypertrophy of the muscular layer and numerous invaginations of mucosal glands in between the muscle bundles.[12-15]

In the present study, we encountered epithelial hyperplasia without metaplasia in 135 cases (6.15%). Mathur et al[16] found adenomatous hyperplasia in 6% cases which is comparable to our results. Mondal et al[17] found adenomatous hyperplasia in 04% cases.

Metaplastic changes in gallbladder are usually of antral or intestinal types. Rarely, neuroendocrine, squamous and pancreatic acinar cell, osseous metaplasias are also seen.[18]

In the present study we observed metaplastic changes in 1043 cases (36.49%). Khanna et al[14] found metaplasia in 32.0% cases. Seretis et al[11] in their study found an overall prevalence of metaplastic features in the resected gallbladder specimens on histopathological examination to be 25.65%.

Metaplasia in the gallbladder showed a female preponderance and a steady increase with age. These findings were in concordance with other studies.[8]

Pseudo pyloric metaplasia came out to be the most common type of metaplastic change in the gallbladder. In our study 923/2858(32.30%) cases showed pseudo pyloric metaplasia. Khanna et al[14]studied pseudo pyloric metaplasia in 16.5% cases. Argon et al[19] found pseudo pyloric metaplasia in 13.2% cases. Albores-Saavedra et al[20]found it in more than 3/4th of the cholecystectomy specimens.

Metaplastic glands are usually present in mucosa but may be quite florid and may infiltrate smooth muscle fibers as well as surrounding nerves mimicking perineural invasion. The lobular arrangement of the metaplastic cells and the small, uniform nuclei help in distinguishing from the adenocarcinoma.

These glands are different from mucus glands in gallbladder in microscopic, histochemical and ultrastructural features but microscopically resemble gastric pyloric glands. Like gastric pyloric glands, metaplastic glands exhibits presence of neutral mucins, but on contrary to gastric pyloric glands, they also show reactivity for sialo- and sulfomucins. That is why they are referred as 'pseudo pyloric' by many researchers. Moreover, metaplastic pseudopyloric glands showing lysozyme immunoreactivity are also positive for class III mucin with paradoxical concanvalin A staining.[21]

Intestinal metaplasia is characterized by the presence of various components such as goblet cells, mucous glands, enterochromaffin cells.[22]In our study we encountered intestinal metaplasia in 112/2858 (3.92%) cases. Mathur et al, found it in 8% cases of cholecystectomies.[16]Khanna et al[14] found it in 15.55% cases.

Usually, only goblet cells are seen which contain sialomucin. Intestinal metaplasia is a much less frequent entity as compared to pyloric gland metaplasia. This metaplasia is incomplete in nature as it lacks the brush border in the background cells. Occasionally, Paneth cells may be seen.[23]

Correlation of intestinal metaplasia in the biliary tract to carcinoma is under research by various researchers.[24,25] Both enterochromaffin cell metaplasia and goblet cell metaplasia is more frequently seen in the cancerous mass than in the control mucosa. The incidence of intestinal metaplasia is significantly raised in gallbladders with dysplasia or carcinomas or gallbladder from high cancer-risk regions. Rarely, massive proliferation of goblet cells is seen in non-neoplastic gallbladders.[8]Intestinal type metaplasia is accompanied byCDX2 expression.[26]

We encountered six cases of squamous metaplasia along with two cases of neuroendocrine type.Presence of neuroendocrine cells, squamous cells, and pancreatic acinar cells has also been reported by researchers in metaplastic gallbladders.[18]

Osseous metaplasia has also been rarely reported.[27]No such case was found in our study.

Dysplastic cases, constituted 88 (3.08%) cases. Dysplastic lesions without adjacent metaplasia were seen in 54 cases i.e. in 1.89% while dysplastic lesions with adjacent metaplasia seen in 34 cases (n=34, 1.19%) Khanna et al[14] found dysplasia in 13% cases. Duarte et al[13] found dysplasia in 16% cases In the present study only 45 cases were found to be malignant out of 2858 cases, i.e. 1.57% cases of the evaluated cholecystectomy specimens in the present study were malignant in nature. Sharma et al[28] diagnosed carcinoma in

1.9% cases which were comparable to our results. A study by Mondal et al[17]showed incidence of 0.6% of Gallbladder carcinoma.

V. Conclusion

Epithelial changes are frequent in the setting of chronic cholecystolithiasis. Cholelithiasis appears to be more frequently associated with metaplastic and dysplastic changes. Most common type of epithelial change seen was metaplasia, followed by hyperplasia. Pseudopyloric type of metaplasia was the commonest type of metaplastic change. Timely resection of symptomatic gallbladder may stop the progression of disease.

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