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Original Research Article

Histopathological changes in cholecystectomy specimens and their association with gallstones

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ABSTRACT

Background: Gallstone disease is associated with a wide range of histopathological changes. Chronic irritation by gallstones can lead to inflammatory, metaplastic and premalignant alterations, some of which may progress to carcinoma. Routine histopathological examination helps to detect these changes and understand their association with gallstones. The study aimed to evaluate the histopathological lesions in cholecystectomy specimens and to assess their association with gallstone type.

Methods: This prospective observational study was conducted in Department of Pathology at a tertiary care center from January 2025 to January 2026.Total of 148 cholecystectomy specimens were included. Clinical details, radiological findings, gross and histopathological findings were studied. Gallstones were categorized as cholesterol, mixed, pigment, or absent. Statistical correlation was calculated using Fisher's exact test and Chi-square with $p<0.05$ considered significant.

Results: Among 148 specimens, 106 (71.6%) were from females and 42 (28.4%) from males. Mean age was 41.8 years (SD 12.22). Gallstones were identified in 128/148 (86.5%) specimens; mixed stones were most frequent (55/148, 37.2%) Chronic calculous cholecystitis was the most common histopathological diagnosis (81/148, 54.7%). Among stone-containing specimens, inflammatory lesions ($\chi^2=16.51$, $p<0.001$), metaplastic lesions ($\chi^2=11.40$, $p=0.003$) and reactive epithelial lesions ($p=0.015$) were significantly associated with stone type. No statistical association was demonstrated for premalignant lesions ($p=0.439$).

Conclusions: In this study, inflammatory and metaplastic lesions showed strong association with gallstones, highlighting the role of chronic irritation in mucosal transformation. Routine histopathological examination of all cholecystectomy specimens helps in detecting premalignant lesions and guiding patient management.

Key words: Cholecystectomy, Gall bladder, Gall stones, Histopathology

INTRODUCTION

The gallbladder is a pear-shaped situated on the inferior surface of the liver and is lined by absorptive columnar epithelium responsible for concentrating bile through active transport of water and electrolytes.[1] Alterations in bile composition, epithelial absorptive function, and gallbladder motility contribute to gallstone formation, which in turn leads to chronic mucosal irritation and a wide spectrum of histopathological changes.[2]

Gallstone disease is among the most common disorders affecting the hepatobiliary system, with a worldwide prevalence of approximately 10–20%.[3] In India, the prevalence ranges from 2–29%, with considerable regional variation.[4] Recent studies indicate an increase in burden of

gall stones likely related to changing dietary patterns and metabolic risk factors.[2,5]

Gallstones vary in their composition and are classified into cholesterol stones, pigment stones (black and brown), and mixed stones.[4] These can be identified easily by their morphology e.g. cholesterol stones are single, oval and yellowish in color, pigmented stones are usually multiple, small and black colored. Mixed stones are multiple, multifaceted and variable size.[6]

Gall stones are responsible for the irritation of the columnar epithelium and are the main underlying cause for a number of histopathological changes like acute and chronic cholecystitis, cholesterolosis, follicular cholecystitis and xanthogranulomatous cholecystitis.[7,8] Long-standing gallstone disease and associated chronic inflammatory response may predispose to epithelial alterations such as pyloric metaplasia, intestinal metaplasia, dysplasia, and incidental carcinoma.[9,10] Therefore, detailed histopathological examination of cholecystectomy specimens is essential not only for identifying the spectrum of gallbladder lesions but also for evaluating their relationship with the presence and type of gallstones.

METHODS

This prospective observational study was conducted in the Department of Pathology at a tertiary center over a period of one year (January 2025 to January 2026). All cholecystectomy specimens received during the study period were included. Autolyzed specimens were excluded from the study. Patients of 11-80 yrs and both genders were included. Relevant clinical details, including presenting symptoms and radiological findings, were noted.

Specimens were fixed in 10% formalin. Detailed gross examinations were done. Four sections were taken, two from the body, one from the neck, and one from the fundus. Additional sections were given when focal lesions were present.4–5 µm thick sections were prepared and stained with hematoxylin and eosin. Detailed histopathological examination (HPE) was done, and predominant lesion was noted in cases with multiple findings.

Gallstones were categorized as cholesterol, mixed, pigment, or absent. Histopathological findings were grouped into inflammatory, hyperplastic, metaplastic, reactive, and premalignant/neoplastic categories. Statistical correlation was performed to obtain the association between histopathological lesions and gallstone type, using Pearson's Chi square and Fisher's exact test, with p value < 0.05 considered significant.

RESULTS

Total 148 cholecystectomy specimens were studied. The age group ranged from 11 to 80yrs. Mean age was 41.8, SD± 12.22036, maximum cases were between 4th to 5th decade of life (33 cases). Female-to-male ratio was 2.5:1(Graph 1)

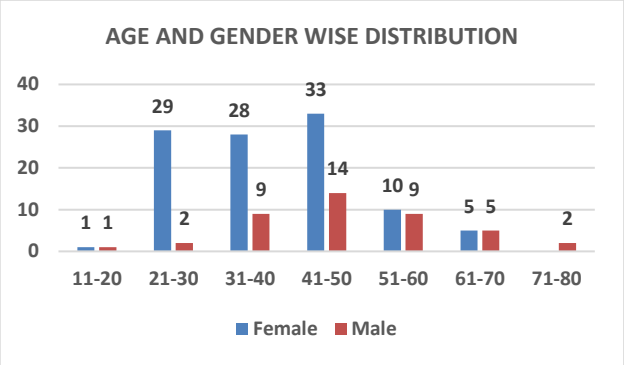


Figure 1: Age and gender distribution.

Table 1: Details of clinical presentation.

Clinical presentation	No. of cases
Pain right hypochondrium	127
Incidental (gall stones on USG)	12
Fever	4
Diffuse pain abdomen	3
Vomiting	1
Epigastric pain	1
Total	148

Most common clinical presentation was pain in the right hypochondrium in 127 cases (83.8%) **(**Table 1). Fever was present in acute cholecystitis and gangrenous cholecystitis. Gall stones were incidental findings in 12 cases in which USG abdomen was performed for other clinical reasons. One case had gall bladder polyp and the other had mass in Gall bladder (GB) on USG both presented with pain in right hypochondrium (Table 1).

Detailed gross examination of 148 specimens was done. The type of stone, number of stones, mucosal findings, wall thickness were noted (Table 2). Gallstones were identified by their morphology e.g. cholesterol stones are single, oval and yellowish in color; pigmented stones are usually multiple, small and black colored; mixed stones are multiple, multifaceted and variable size (Figure 2). Gall stones were present in 128/148 (86.5%) cases, with mixed stones being the most common (55/148, 37.2%) followed by cholesterol (43/148, 29.1%) and pigment stones (30/148, 20.3%). 20 specimens showed no stones. Multiple stones (50.6%) were more common.



Figure 2: Gross picture: cut open Gall bladder showing multiple multifaceted and irregular mixed stones.

Mucosa showed strawberry gall bladder in 10 cases, polyps were seen in 8cases which turned out to be cholesterol polyps and Intracholecystic papillary neoplasms (ICPN) on HPE. ICPN on gross appear as prominent exophytic growth within the gallbladder (Figure 3) or granular, friable soft tan excrescences.

Acute cholecystitis, gangrenous cholecystitis showed denuded mucosa (Table 2) Wall thickness was >3mm in cases of adenomyoma, adenomyomatous hyperplasia, follicular cholecystitis, xanthogranulomatous cholecystitis, acute on chronic cholecystitis and few cases of chronic calculous cholecystitis on HPE (Table 2).

Extensive microscopic examination was done for histopathological lesions and their association with gall stones were studied (Table 4 and 5). Predominant findings were mentioned if there are multiple findings on HPE

Chronic cholecystitis was the common histopathological finding seen in 81cases (54.7%) with stones and 10cases without stones (Table 3). Acute cholecystitis characterized by erosion of mucosa and edema of lamina propria (Figure 4A) was observed in 2 cases. Acute inflammatory changes were also seen acute on chronic cholecystitis and gangrenous cholecystitis in which necrosis was also seen.



Figure 3: Gross picture: cut open gall bladder showing an exophytic growth measuring 1.2×1 cms arising from the mucosa in a case of Intracholecystic papillary neoplasm (ICPN).

Table 2: On gross examination findings of the cholecystectomy specimens.

Gross examination findings	No. of cases
Type of gallstones (cholesterol/ pigment/ mixed/no stone)	43/30/55/20
No. of Stones(single/two/multiple)	38/15/75
Gall bladder wall thickness(<3mmm/>3mm)	124/24
Mucosal lesions (denuded/cholesterolosis/polyp)	12/10/8

Table 3: Number of histopathology lesion according to gender.

HPE Findings	F	M	Total	Percentage (%)
Acalculous Chronic Cholecystitis	10	0	10	6.8%
Acute on Chronic Cholecystitis	2	0	2	1.4%
Adenomyoma	1	0	1	0.7%
Adenomyomatous hyperplasia	2	0	2	1.4%
Cholesterolosis	11	1	12	8.1%
Cholesterol polyp	2	1	3	2.0%
Chronic Calculous Cholecystitis	52	29	81	54.7%
Follicular Cholecystitis	0	2	2	1.4%
Gangrenous Cholecystitis	1	1	2	1.4%
Gastric Metaplasia	21	5	26	17.6%
ICPN - foveolar / pyloric type	2	1	3	2.0%
ICPN with low grade dysplasia	1	1	2	1.4%
Xanthogranulomatous Cholecystitis	1	1	2	1.4%
Total	106	42	148	100%

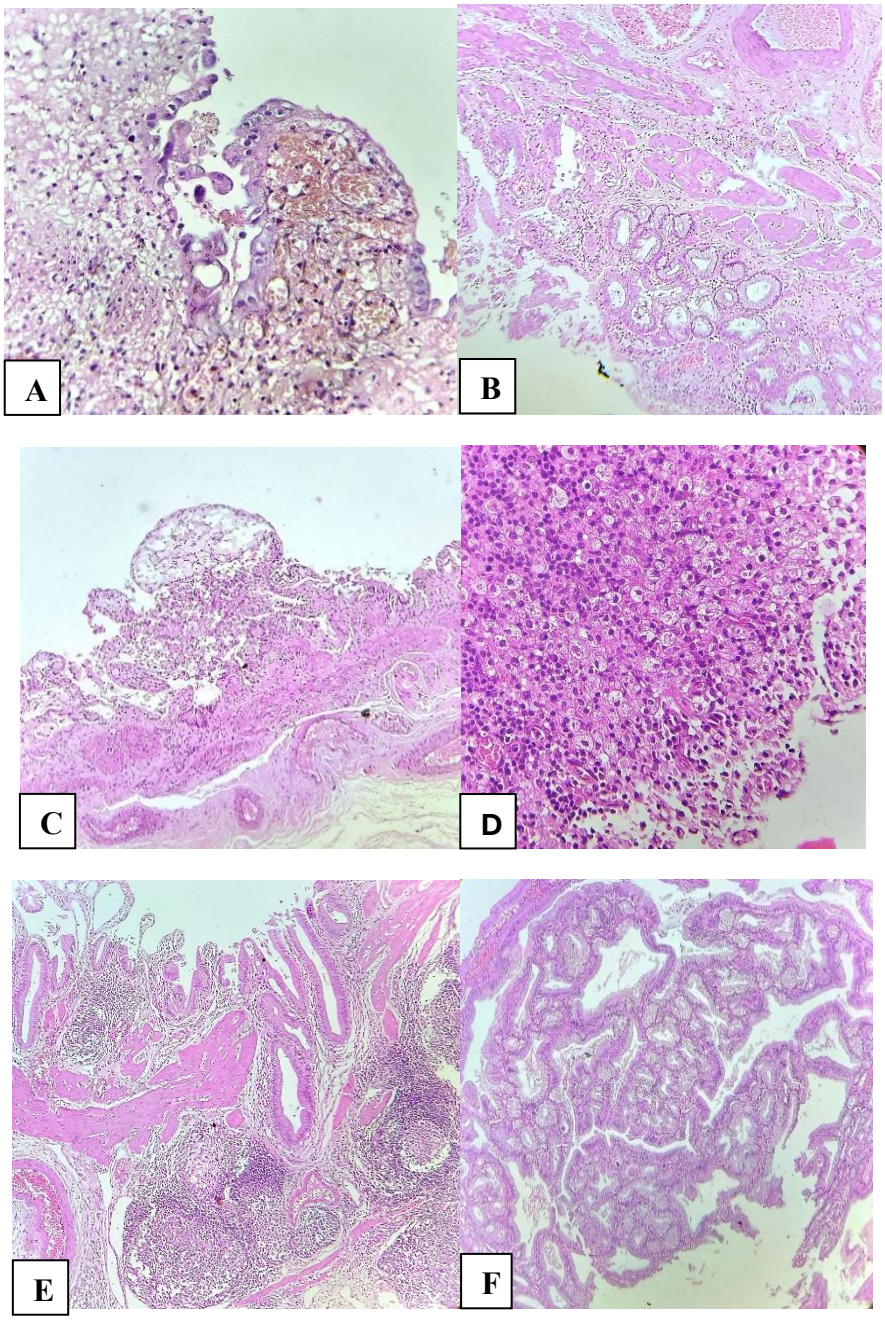


Figure 4: Microscopic Images of various histopathological lesion in cholecystectomy specimens. (A) Section shows ulcerated mucosa in a case of Acute cholecystitis(H&E 400X); (B) section shows Pyloric metaplasia(H&E 100X); (C) section shows collection of foamy macrophages with in the mucosa representing Cholesterolosis (H&E 100X); (D) section shows foamy histiocytes and chronic inflammatory infiltrate in Xanthogranulomatous cholecystitis(H&E 400X); (E) section shows follicles with prominent germinal centre in muscularis mucosa - Follicular cholecystitis(H&E 100X); (F) section shows mucinous glands arranged back to back in Intracholecystic papillary neoplasm((H&E 100X).

Gastric metaplasia is a change of biliary epithelium to either pyloric type epithelium showing cuboidal epithelium **(**Figure 4B) or foveolar type showing voluminous mucinous epithelium**.** It was identified in 26 cases (17.6%), predominantly in females (21 cases), and was commonly associated with chronic cholecystitis. Cholesterolosis seen as accumulation of foamy macrophages in laminapropria **(**Figure 4C) was observed in 12 cases, while cholesterol polyps were noted in three cases. Cholesterolosis was commonly associated with cholesterol stone. Adenomyoma and adenomyomatous hyperplasia were uncommon.

Xanthogranulomatous cholecystitis a chronic, focal or diffuse fibroinflammatory process resulting from an intramural accumulation of foamy histiocytes (Figure 4D**)** was observed in 2 cases, only one was associated with gall

stone(pigment). Follicular cholecystitis, a rare entity is characterized by prominent lymphoid follicles with lymphoid hyperplasia and germinal centers **(**Figure 4E**)** present was observed in two cases, both occurring in male patients and were associated with pigment stones (Table 3 and 4).

Intracholecystic papillary neoplasm (ICPN) on microscopy shows back-to-back epithelial units in papillary, tubular or tubulopapillary configuration with limited stroma.4 morphological patterns are recognized i.e biliary, gastric including pyloric (Figure 4F**)** and foveolar type, intestinal and oncocytic type. It was noted in five cases (3.4%). These included ICPN-foveolar type with cholesterolosis (one case), ICPN- pyloric type (two cases), and ICPN with low-grade dysplasia (two cases).

The Gall bladder lesions were further categorized as inflammatory, hyperplasia, metaplasia, reactive epithelial changes and premalignant lesions. Inflammatory lesions included acute, chronic changes and xanthogranulomatous inflammation. Reactive epithelial changes included Cholesterolosis and cholesterol polyp. The association between histopathological lesions and gallstone type assessed using the Pearson chi-square test or Fisher's exact test, as appropriate (Table-5). The statistically significant association was observed between inflammatory lesions and gallstone type (χ^2=16.51, p<0.001), with inflammatory lesion more frequent in specimens with mixed stones. Metaplastic changes which are precursor of malignancy also demonstrated a significant association with gallstones (χ^2=11.40, p=0.003) especially pigment stones .Reactive epithelial alterations like cholesterolosis and cholesterol polyp showed statistically significant association with cholesterol stones(Fisher's exact test**,** p=0.015).In contrast, no statistically significant association was found between hyperplasia (Fisher's exact test, p=0.510) as well as Premalignant lesions such as ICPN with gall stone type (Fisher's exact test, p=0.439)

Table 4: Association of gall bladder lesion with presence and absence of gall stones.

Mucosal lesion	No stones	cholest	mixed	pigment	Total
Acute chronic cholecystitis	1	0	0	1	2
Chronic cholecystitis	10	22	47	12	91
Ccc with adenomyoma	0	1	0	0	1
Adenomyomotous hyperplasia	0	1	1	0	2
Chl & cholesterol polyp	2	9	2	2	15
Follicular cholecystitis	0	0	0	2	2
Gangrenous	0	1	1	0	2
Gastric metaplasia	3	8	4	11	26
ICPN -foveloar/pyloric type with CHL	3	1	0	1	5
Xanthogranulomatous inflammation	1	0	0	1	2
Grand total	20	43	55	30	148

Table 5: Statistical analysis to understand the association of type of gall stone with gall bladder lesions.

Histopathological lesion	Mixed stone N (%)	Cholesterol stone N (%)	Pigment stone N (%)	Fisher/ χ^2	P value
Inflammatory	48 (87.3)	23 (53.5)	16 (53.3)	16.51	<0.001*
Hyperplasia	2 (3.6)	2 (4.7)	0 (0.0)	fisher	0.510
Metaplasia	4 (7.3)	8 (18.6)	11 (36.7)	11.40	0.003
Reactive	2 (3.6)	9 (20.9)	2 (6.7)	fisher	0.015
Premalignant	0 (0.0)	1 (2.3)	1 (3.3)	fisher	0.439

DISCUSSION

Gallbladder lesions show a wide histopathological spectrum; most commonly associated with cholelithiasis. Histopathological examination of cholecystectomy specimens remains essential for identifying inflammatory, metaplastic, pre-neoplastic lesions and malignant lesions that are often clinically unsuspected.

In the present study, female predominance (female-to-male ratio 2.5:1) was observed, in concordance with findings reported by Mohan et al, Raja et al, Gupta et al and Singh et al.[4,11-13] Most cases occurred in the fourth and fifth decades, similar to observations in the above studies, reflecting the cumulative effect of long-standing gallstone disease.

Gallstones were present in 86.5% of cases in the present study, with mixed stones (37.2%) being the predominant type. This is comparable to observations by Mohan et al, Singh et al, Pandey et al i.e. 62.3%; 54%;72.4%.[11,13,14] The study observed multiple stones (50.6%) were more common. Singh et al found similar finding suggesting symptomatic gall bladder disease was more frequent with multiple stones.[13]

Chronic calculous cholecystitis was the most common histopathological diagnosis (54.7%), comparable to reports of Raja et al, Singh et al, though slightly lower than rates reported by Mohan et al.[4,11,13] In this study, a strong association between gallstones and chronic inflammatory lesions of the gallbladder particularly mixed stones was noted. Singh et al found chronic cholecystitis was more common with mixed stones, though statistical association couldn't be established in their study.[13] Acute inflammatory changes were infrequent, similar to findings by Singh et al, Sharma et al.[13,15]

Gastric metaplasia was identified in 17.6% of cases, similar frequencies were reported by Gupta et al[12] i.e. 19.2%. In our study, it was statistically associated with pigment stone whereas Areeba Nasar et al, Agarwal et al reported association with cholesterol stones and mixed stones respectively.[16,17] A possible explanation was given by Elfving et al that metaplastic changes are considered adaptive responses and could be due to mechanical irritation by caliculi.[18]

Xanthogranulomatous cholecystitis often mimics Gallbladder carcinoma intraoperatively and presents with pericholecystic infiltration and hepatic involvement.[19] Its diagnosis therefore remains elusive, emphasizing the importance of histopathological differentiation from carcinoma. In present study, in one case radical cholecystectomy was performed but there was no hepatic involvement. It constituted 2.0% of cases, comparable to incidences reported by Mohan et al, Gupta et al i.e 2.3% and 2.7%. of particular significance.[11,12]

Intracholecystic papillary neoplasm (ICPN) was identified in 5cases (3.4%) of which 2 cases had no clinical suspicion but were incidental findings on HPE. This underscores the importance of detailed histopathological examination of these specimens. We found no statistical association of ICPN with gall stones. This could be due to small number of cases. Gupta et al found dysplasia and Gall bladder carcinoma to be associated with gall stones. Datta et al also found similar findings.[12,20]

Limitation of study

Radiological findings were not available in all cases hence a radiological correlation was not possible.

CONCLUSION

This study found an association between inflammatory lesions and mixed stones, while metaplastic changes were significantly associated with pigment stones. Cholesterolosis was associated with all three types of stones. Premalignant lesions like ICPN were incidental finding on HPE without prior clinical suspicion and showed no statistically significant association with gall stones. We conclude that a thorough histopathological examination is recommended to identify significant pathological changes, especially metaplastic lesions and premalignant lesions.

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