



Original Article

## Beyond Gallstones: Histopathological Spectrum and Diagnostic Challenges in Routine Cholecystectomy Specimens

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Received: 23-02-2026

Accepted: 13-03-2026

Available online: 27-03-2026

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Medical and Pharmaceutical Research

### ABSTRACT

**Background:** Cholecystectomy is one of the most frequently performed surgical procedures, primarily for gallstone disease. Although many gallbladder specimens show inflammatory pathology, routine histopathological examination reveals a wide spectrum of lesions ranging from reactive and metaplastic changes to premalignant conditions. Several of these entities pose diagnostic challenges due to overlapping histomorphological features.

**Objectives:** To evaluate the histopathological spectrum of gallbladder lesions in routine cholecystectomy specimens and to highlight diagnostically challenging lesions and their histological mimics.

**Materials and Methods:** This hospital-based observational study was conducted in the Department of Pathology, Saraswathi Institute of Medical Sciences, Hapur, over six months (January 2025–June 2025). A total of 151 gallbladder specimens obtained following laparoscopic or open cholecystectomy were studied. Specimens were fixed in 10% neutral buffered formalin, routinely processed, and examined using hematoxylin and eosin–stained sections. Histopathological findings were analyzed with respect to age, gender, gross features, and microscopic diagnosis.

**Results:** The study included 151 patients with a marked female predominance (male: female = 1:8.4). The mean age was 37.3 years, with the highest number of cases occurring in the fourth decade of life. Chronic cholecystitis was the most common diagnosis (40.3%), followed by cholesterolosis (13.9%), pyloric metaplasia (11.9%), adenomyomatous hyperplasia (9.2%), and intestinal metaplasia (7.2%). Reactive atypia was observed in 6.6% of cases, posing a potential diagnostic pitfall. Less frequent lesions included xanthogranulomatous, follicular, eosinophilic, and hyalinizing cholecystitis. Increased gallbladder wall thickness was noted in one-third of cases and was commonly associated with chronic inflammatory and hyperplastic lesions.

**Conclusion:** Routine histopathological examination of all cholecystectomy specimens is essential, as it reveals a broad spectrum of lesions beyond gallstones, some of which may mimic malignancy or represent potential precursors. Careful histomorphological assessment and adequate sampling are crucial to avoid misdiagnosis and ensure appropriate patient management.

**Keywords:** Gallbladder, Cholecystectomy, Chronic cholecystitis, Metaplasia, Diagnostic challenges, Histopathology.

### INTRODUCTION

The gallbladder is among the most common surgically resected organs, and the number of cholecystectomies have increased significantly in the last decade [1]. While the majority of cholecystectomies are performed for gallstone disease, routine histopathological examination of cholecystectomy specimens can uncover various lesions. These range from

reactive to metaplastic, premalignant, and even malignant transformations [2,3]. Some of these lesions pose diagnostic challenges due to overlapping histological features and may be underdiagnosed or misdiagnosed [4].

In addition, a remarkable association has been found between dysplasia and intestinal metaplasia, pyloric metaplasia, and adenomyomatous hyperplasia, which can be distinguished mainly based on histomorphological features [5]. Accurate distinction between reactive atypia, dysplasia, and their mimics remains crucial for appropriate patient management [6].

## MATERIALS AND METHOD

This hospital-based observational study was conducted in the Department of Pathology, Saraswathi Institute of Medical Sciences (SIMS), Hapur, Uttar Pradesh, over a period of six months from January 2025 to June 2025. All gallbladder specimens received from the Department of Surgery during this period were included and evaluated.

**Inclusion criteria:** All gallbladder specimens from patients of any age and gender submitted for histopathological examination.

**Exclusion criteria:** Autolysed specimens with compromised histomorphology.

A total of 151 cholecystectomy specimens obtained from patients undergoing either laparoscopic or open cholecystectomy were studied. Specimens were received in 10% neutral buffered formalin and subjected to routine gross examination, with particular attention to gallbladder wall thickness and mucosal abnormalities. After adequate fixation, representative tissue sections were processed routinely, embedded in paraffin, and 3–5 µm thick sections were stained with hematoxylin and eosin (H&E). Histopathological evaluation was performed to identify inflammatory, metaplastic, hyperplastic, and other non-neoplastic lesions. Data were analyzed using descriptive statistics. Categorical variables were expressed as percentages

## RESULTS

The study population comprised 151 patients, with a marked female predominance. Females constituted 135 cases (89.4%), while males accounted for 16 cases (10.6%), yielding a male-to-female ratio of 1:8.4. The majority of cases were observed in the 31–40-year age group (35.1%), followed by the 20–30-year (25.2%) and 41–50-year (22.5%) age groups (Table 1). Gallbladder lesions were relatively uncommon at the extremes of age.

**Table 1 Age and gender wise distribution of study participants**

Age group	Male	Female	Total	Percentage (%)
≤20	1	3	4	2.6%
20-30	5	33	38	25.2%
31-40	2	51	53	35.1%
41-50	3	31	34	22.5%
51-60	5	17	22	12.6%
Total	16	135	151	100%

On macroscopic examination, increased gallbladder wall thickness (>3 mm) was noted in 50 cases (33.1%), while 101 cases (66.9%) showed wall thickness within normal limits. Increased wall thickness was more commonly associated with chronic inflammatory and hyperplastic lesions (Table 2)

**Table 2 Distribution of cases according to the wall thickness (on macroscopic examination)**

Wall thickness	Number of cases (Total cases N= 151)	Percentage(%)
Increased (> 3 mm)	50	33.1%
Normal (≤3mm)	101	66.9%
TOTAL	151	100%

Chronic cholecystitis was the most frequent histopathological diagnosis, identified in 61 cases (40.3%). This was followed by cholesterolosis in 21 cases (13.9%) and pyloric metaplasia in 18 cases (11.9%). Intestinal metaplasia was observed in 11 cases (7.2%), while adenomyomatous hyperplasia accounted for 14 cases (9.2%). Acute cholecystitis was diagnosed in 8 cases (5.2%). Less common entities included xanthogranulomatous cholecystitis (1.9%), follicular cholecystitis (1.9%), and rare variants such as hyalinizing and eosinophilic cholecystitis (0.6% each) (Table 3)

**Table 3 Distribution of Histopathological Diagnosis in Gall Bladder Lesions**

Histopathological diagnosis	Frequency	Percentage (%)
Chronic cholecystitis	61	40.3%
Chronic cholecystitis with Reactive atypia	10	6.6%
Cholesterolosis	21	13.9%
Pyloric metaplasia	18	11.9%

Intestinal metaplasia	11	7.2%
Acute cholecystitis	8	5.2%
Adenomyomatous hyperplasia	14	9.2%
Xanthogranulomatous cholecystitis	03	1.9%
Hyalinizing cholecystitis	01	0.6%
Eosinophilic cholecystitis	01	0.6%
Follicular cholecystitis	03	1.9%

## DISCUSSION

In the present study, gallbladder diseases were most frequently encountered in the fourth decade of life, accounting for 35.1% of cases, followed by the third (25.2%) and fifth decades (22.5%). The mean age of the study population was 37.3 years, which is comparable to the findings of Banerjee et al., who reported a mean age of 39.3 years [7]. This similarity suggests a consistent age-related pattern in the occurrence of gallbladder pathology, underscoring the influence of age as an important factor in disease development.

In Haldar's study, the male-to-female ratio was 1:3.5 [8]. In contrast, in the present study, it was 1:8.4. This variation suggests differences in gender distribution, potentially due to demographic differences or recruitment methodologies.

Table 4 presents a comparison of the histopathological spectrum observed in the present study with findings from selected published studies. Across most series, chronic cholecystitis emerges as the predominant diagnosis, highlighting the inflammatory nature of gallbladder pathology in routine cholecystectomy specimens. The proportion of chronic cholecystitis in the present study (40.3%) is lower than that reported by Haldar et al., Noor et al. Sood et al., Talreja et al., and Sharma et al. [8, 9, 10, 11, 12], possibly reflecting differences in case selection and reporting of associated metaplastic and hyperplastic changes. The majority of cases diagnosed as chronic cholecystitis showed the presence of chronic inflammatory cell infiltrate, denuded mucosa with Rokitansky-Aschoff sinuses, and fibrous wall thickening.

**Table 4** Comparative distribution of major histopathological lesions in gallbladder across selected studies

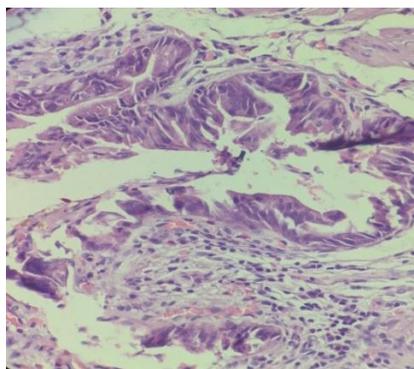
Histopathological diagnosis	Present study (%)	Haldar et al (%)	Noor et al (%)	Sharma R et al (%)	Sood et al (%)	Talreja et al (%)
Chronic cholecystitis (with or without reactive atypia)	46.9	72.9	55.0	–	91.5	78.4
Metaplastic lesions (pyloric and/or intestinal)	19.1*	16.6	25.0	33.6	–	0.7
Cholesterosis	13.9	2.5	7.5	–	1.7	12.1
Adenomyomatosis / adenomatous hyperplasia	9.2	–	3.3	–	1.1	–
Acute cholecystitis	5.2	3.8	6.6	–	3.3	6.3
Other inflammatory variants †	5.0	3.3	1.6	2.5	1.6	1.2

\* Metaplastic lesions include pyloric metaplasia (11.9%) and intestinal metaplasia (7.2%) in the present study.

† Other inflammatory variants include xanthogranulomatous, follicular, eosinophilic, and hyalinizing cholecystitis.

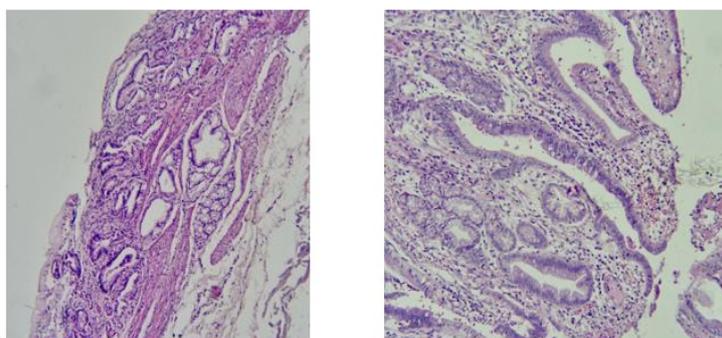
**Note:** Variations in lesion frequencies across studies reflect differences in sample size, inclusion criteria, diagnostic thresholds, and reporting practices. Some studies have reported chronic cholecystitis with associated reactive atypia and metaplastic changes as a single category, while others have documented these entities separately.

One of the most important diagnostic challenges encountered in gallbladder pathology is the distinction between reactive atypia and early invasive carcinoma, which constituted 10 cases (6.6%) in the present study. Reactive atypia, particularly within Rokitansky-Aschoff sinuses, may exhibit cytological features such as nuclear enlargement and prominent nucleoli, which can raise concern for malignancy (fig. 1). However, architectural preservation remains the most reliable discriminator. In reactive atypia, the glandular arrangement remains orderly, with maintenance of lobular configuration, absence of infiltrative growth, and lack of desmoplastic stromal response. Recognition of these architectural features is critical to avoid overdiagnosis of carcinoma and unnecessary clinical intervention.



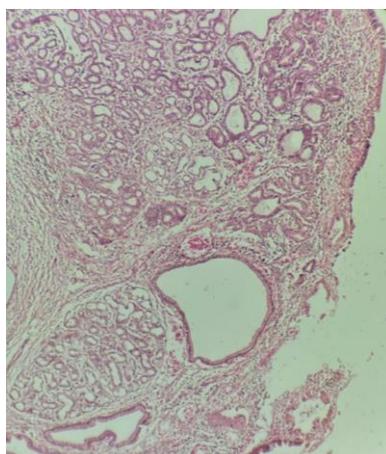
**Fig 1: Chronic cholecystitis showing reactive atypia- disorganized cells with overlapping and prominent nucleoli (H&E, 400X)**

Metaplastic lesions constituted a significant proportion of cases. Pyloric metaplasia (fig 2), observed in 11.9% of cases, represents a common adaptive response to chronic inflammation. Florid pyloric metaplasia extending deep into the gallbladder wall can pose diagnostic difficulty by mimicking invasive glands. Recognition of uniform cytology, orderly glandular architecture, and absence of dysplasia is essential to avoid overdiagnosis. Intestinal metaplasia was detected in 7.2% of cases and was characterized by the presence of goblet cells. This lesion warrants careful documentation, as several studies have suggested a potential association between intestinal metaplasia, dysplasia, and gallbladder carcinoma. Thorough sampling of such cases is therefore crucial. Metaplastic changes, particularly intestinal metaplasia, are considered part of the metaplasia–dysplasia–carcinoma sequence and therefore warrant careful evaluation.



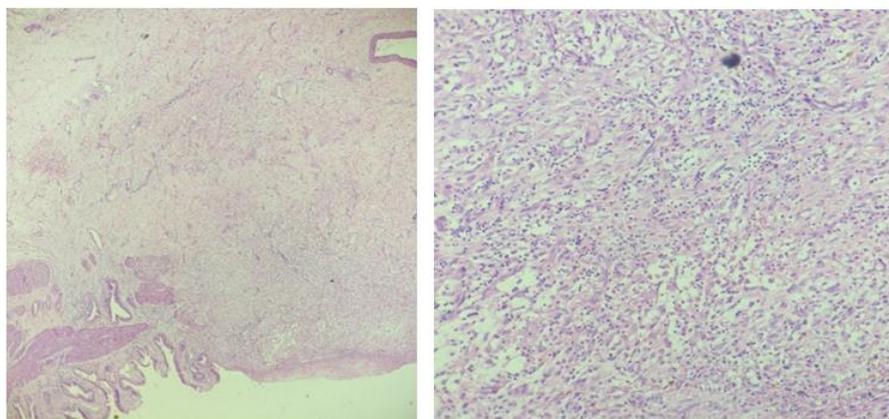
**Fig-2 (a, b) Pyloric metaplasia – Showing tubular arrangement with columnar mucin containing cells. (H&E, 100X and 400X)**

Adenomyomatous hyperplasia accounted for 9.2% of cases and remains another important mimic of malignancy. Thickened wall on gross examination and pseudo-invasive glands associated with smooth muscle hyperplasia on microscopic evaluation can closely resemble adenocarcinoma, particularly in the background of chronic cholecystitis (fig. 3). Awareness of this entity and its characteristic histological features help prevent misinterpretation and unnecessary further intervention [13,14].



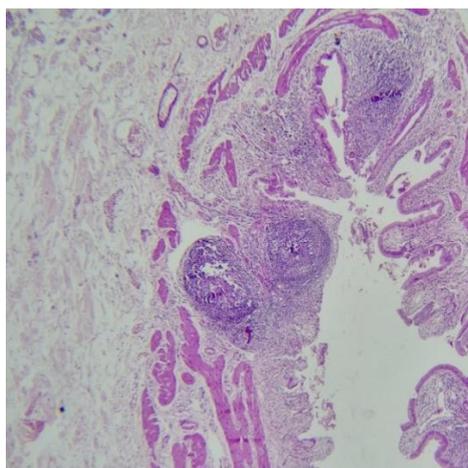
**Fig 3- Adenomyomatous hyperplasia of gall bladder showing dilated and hyperplastic mucosal glands extending into the muscular layer. (H&E, 100X)**

Xanthogranulomatous cholecystitis, although infrequent in the present study, represents a well-recognized diagnostic pitfall due to marked wall thickening and dense inflammatory infiltrates with foamy macrophages (fig. 4). In the present study, three cases (1.9%) were observed, similar to findings reported by Sood et al. and Talreja et al. [10,11]

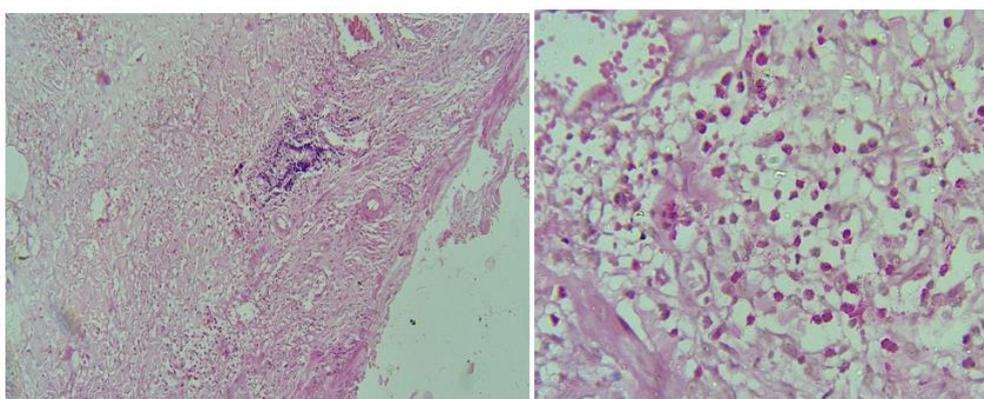


**Fig-4 Xanthogranulomatous cholecystitis: (a) Thickened wall showing diffuse infiltration of foamy histiocytes (H&E 40X), (b) Foamy macrophages along with chronic inflammatory cell infiltrate (H&E, 400X) .**

Cholesterosis, seen in 21 cases (13.9%) showed collections of foamy macrophages in the lamina propria. Their importance remains unclear but association with metabolic disorder has been suggested [15,16,17]. However, it is not considered a premalignant lesion [18]. Similarly, rare lesions such as follicular (fig 5), eosinophilic (fig 6), and hyalinizing cholecystitis emphasize the wide histopathological spectrum encountered in routine practice.



**Fig-5 Follicular cholecystitis- showing lymphoid follicles (H&E, 100X)**



**Fig-6 (a, b) Eosinophilic cholecystitis showing infiltration of gall bladder wall by eosinophils (H&E, 100X and 400X)**

The present study is limited by its relatively small sample size and lack of ancillary techniques such as immunohistochemistry and molecular analysis.

Overall, the findings underscore the importance of meticulous grossing, adequate sampling, and careful histomorphological assessment in gallbladder specimens. Routine histopathological examination remains indispensable for identifying diagnostically challenging lesions and ensuring accurate differentiation between benign, premalignant, and malignant conditions. Such findings reinforce the indispensable role of routine histopathology in detecting subtle yet clinically significant lesions.

## CONCLUSION

Routine histopathological examination of all cholecystectomy specimens is strongly recommended, as it enables detection of a wide spectrum of lesions, including premalignant conditions and mimics of malignancy, thereby preventing diagnostic errors and guiding appropriate clinical management.

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