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Clinicopathological Correlation of Gallstones Characteristics with Histopathological Spectrum of Gallbladder Lesions

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ABSTRACT

Background: Gallbladder lesions can be both inflammatory and malignant (including neoplastic), constituting a wide spectrum of disease. Cholelithiasis is one of the commonest diseases of the gall bladder and has many histopathological changes associated with it. The characterization of gallbladder lesions along with gallstones can give valuable data on their clinicopathologic association. **Aim:** To study the clinicopathological profile of gallbladder lesions and to analyse the gallstone characteristics associated with them in cholecystectomy specimens. **Materials and Methods:** Over a period of two years, a retrospective study of 210 cholecystectomy specimens, received for histopathological examination, was conducted. The evaluated parameters included demographic details, histopathological diagnosis, number and type of gallstones, colour of gallstones, gallbladder wall thickness and so on. A histopathological study was done through routine stain. Hematoxylin and eosin stain was used. Statistical analysis was done to find out clinicopathological associations. **Results:** Of the total 210 cases studied, females formed 70.95% of the study population. The majority of gallbladder lesions had their peak incidence in the third and fourth decades of life. The most common histopathological lesion was chronic calculous cholecystitis, seen in 185 (88.1%) cases. Malignant lesions were seen in 8 (3.8%) cases. The majority of the gallstones were multiple gallstones and solitary stones were the least encountered ones. Also, mixed stones were seen to be the most common morphological type of gallstones among the gallstone patients. Statistical analysis showed a significant association between age and histopathological diagnosis, whereas age showed no significant association with stone number, stone type, stone colour, and gallbladder wall thickness. **Conclusion:** The most common lesion of the gallbladder is chronic calculous cholecystitis, which is often associated with multiple mixed gallstones. Routine histopathological examination of every cholecystectomy specimen is necessary to pick up the entire range of gall bladder lesions including incidental premalignant and malignant lesions. The gallstone characteristics assessment may shed further light on the pathologic changes of the gallbladder.

Keywords*: Gallbladder lesions; Cholelithiasis; Chronic calculous cholecystitis; Gallstones; Histopathology; Gallbladder carcinoma.*

INTRODUCTION

Gallbladder diseases are a major health burden worldwide and are one of the commonest causes of gastrointestinal morbidity requiring surgical intervention. The gallbladder is crucial for the storage, concentration, and timed release of bile to help digest and absorb fats in the diet. Diseases of the gallbladder may include inflammatory and hyperplastic conditions as well as pre-malignant and malignant neoplasm. The most prevalent disorder among these conditions is cholelithiasis, which is commonly associated with a wide range of histopathological changes in gallbladder mucosa.[3,4]

The condition of gallstones can be considered common and vary based on demographic or geographic region. As age rises, this comes more common and is more reported in females than males.[1,2] Gallstone formation is a complex, multifactorial process that involves an abnormality of bile, nucleation of cholesterol crystals, impaired gallbladder motility, and inflammation. Based on morphological and chemical characteristics of gallstones, they can be classified as cholesterol, pigment, mixed, or combined stones. Depending on the pathology of the stone these will vary in number, size, colour, and composition, and so may the gallbladder wall.[4,16]

Gallstones causes chronic irritation and inflammation that can lead to a variety of histopathological lesions. The most frequently occurring lesion in cholecystectomy specimens is chronic calculous cholecystitis, which exhibits varying degrees of atrophy of the mucosa with fibrosis, infiltration of chronic inflammatory cells and formation of the Rokitansky–Aschoff sinuses. Gallstone disease can have a number of complications, including cholesterolosis, xanthogranulomatous cholecystitis, follicular cholecystitis, adenomatous hyperplasia, and metaplastic changes, among others.[15,18,20] A possible pathway in gallbladder carcinogenesis has been proposed as chronic inflammation to epithelial metaplasia to dysplasia to carcinoma.[11,14]

Gallbladder cancer is one of the most aggressive biliary cancers, though it is rare. These cancers are associated with poor clinical prognosis due to clinical presentation late. Epidemiological investigations attribute a considerable association of gallbladder carcinoma with chronic gallstone disease. As a result, the routine histopathological examination of all cholecystectomy specimens is needed for not only verification of clinical diagnosis but also for the identification of incidental premalignant and malignant lesions.[14,18]

Studying the features of gallstones along with a histopathological study provides an insight into the clinicopathological behaviour of gallbladder diseases. Prior research has indicated possible connections between stone type and shape and particular types of mucosal changes and pathology. Nevertheless, in the Indian populace, where gallstone disease is prevalent, the association between the morphology of gallstones and the varying spectrum of gallbladder lesions is hardly understood.[15,16,17,18,20]

A retrospective analysis was carried out on gallbladder lesions in cholecystectomy specimens to study their clinicopathological profile along with the characteristics of gallstones. Through the study of demographic patterns, histopathological diagnosis, stone morphology and related clinicopathological parameters, the study aimed to enhance the understanding of gallbladder pathology and strengthen the rationale for histopathological examination of all cholecystectomy specimens.

MATERIALS AND METHODS

This retrospective study was carried out in the Department of Pathology of a tertiary care teaching hospital from a time period and comprised 210 samples of cholecystectomy received for histopathological examination. Data pertaining to clinical and demographic specifications such as age, sex, clinical diagnosis, imaging findings, and laboratory investigations was obtained from records of the hospital and analysed.

The study included cholecystectomy specimens with a diagnosis of gallbladder disease and presence of cholelithiasis. We excluded specimens that were self-digested, belonging to the pediatric age group, and archived by pathology. Patients in this study had an age range of 12–80 years.

All specimens were stabilized in ten percent formalin and underwent detailed gross examination. Data regarding the dimensions, external surface characteristics, wall thickness, mucosal appearance and the presence of gallstones was collected. Gallstones were analyzed for quantity, morphological type, and colour. Tissue sections were taken from the fundus, body and neck of the gallbladder along with any abnormal lesion (if applicable).

The tissue samples were handled with routine histopathological procedure. Sections of about 5 μm thickness were cut by rotary microtome and stained with routine Hematoxylin and Eosin stain. They used special stains where needed to confirm diagnosis. A histopathological examination was done to identify gall-bladder lesions and their associated mucosal change. Histopathological findings were correlated with demographic variables and gallstones. Gallbladder lesions were categorized according to the final microscopic diagnosis. The data were assembled and analysed statistically to evaluate the clinicopathological associations of age, sex and histopathological diagnosis; number, type and colour of gallstones; and gallbladder wall thickness. The results were statistically significant if p-value is < 0.05

RESULTS

The study encompassed 210 cholecystectomy specimens. The patients were evaluated clinicopathologically concerning their demographic, histopathological, and gallstone features.

Table 1. Demographic Profile of Patients

Variable	Frequency (n=210)	Percentage (%)
Age Group (Years)		
0–20	5	2.4
21–40	94	44.8
41–60	76	36.2
>60	35	16.6
Gender		
Female	149	70.95
Male	61	29.05

The patients' age ranged from less than 20 years to more than 60 years. The 21 and 40 years age group had the maximum number of cases, which was found to be 94–44.8 %. The second number of cases was in the 41 and 60 years age group which was 76–36.2 %. Out of the 210 cases studied, 35 cases (16.6%) belonged to patients older than 60 years, while 5 cases (2.4%) were below 20 years of age. According to the findings, gallbladder lesions were most often noted in the third and fourth decades of life. There were many more female participants than males. Out of the 210 cases, 149 patients (70.95%) were females and 61 patients (29.05%) were males, which gave a female to male ratio of 2.4:1 approximately.

Table 2. Histopathological Spectrum of Gallbladder Lesions

Histopathological Diagnosis	Frequency
Chronic calculous cholecystitis	185
Malignancy	8
Acute cholecystitis	4
Cholesterolosis	4
Xanthogranulomatous cholecystitis	2
Adenomatous hyperplasia	1
Acalculous cholecystitis	1
Chronic cholecystitis	1
Follicular cholecystitis	1
Hyperplastic polyp with chronic cholecystitis	1
Chronic calculous cholecystitis with choledochal cyst	1
Pseudocyst with chronic calculous cholecystitis	1
Total	**210**

Histopathological examination presented a variety of gallbladder lesions. The most commonly diagnosed lesion in 185 (88.1%) cases was chronic calculous cholecystitis. Eight cases (3.8%) were malignant.

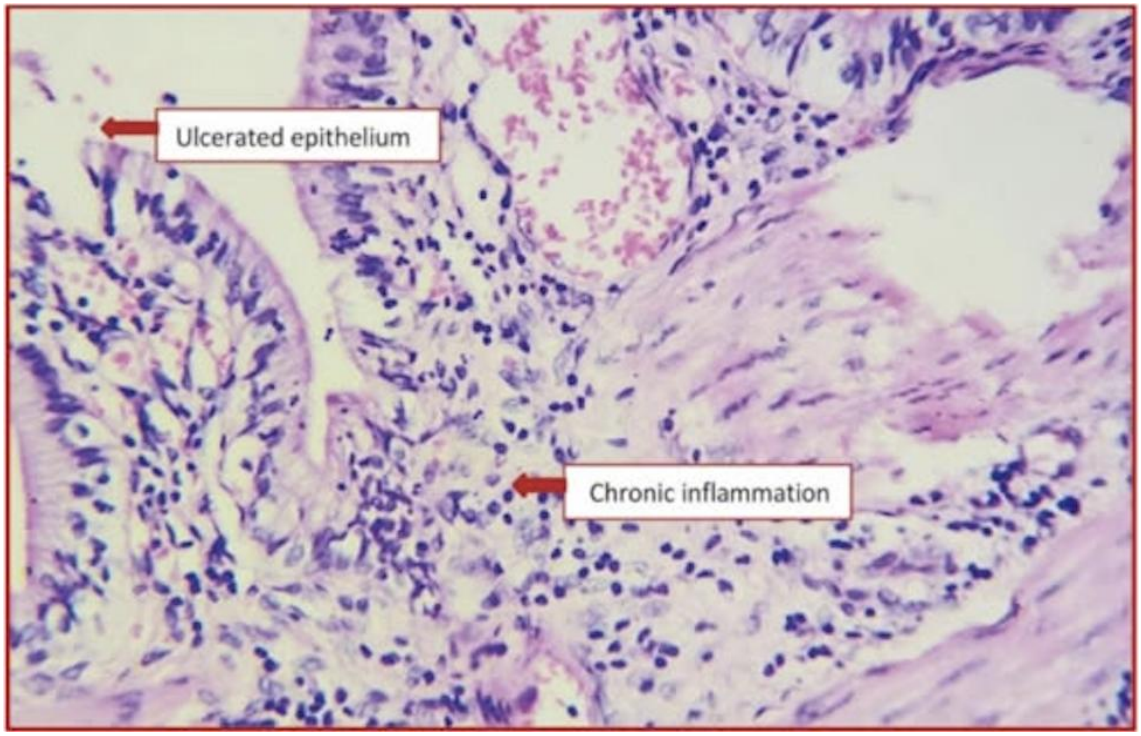


Figure 1. *Histopathological photomicrograph showing chronic calculous cholecystitis with ulcerated epithelium and chronic inflammatory cell infiltrate (H&E stain, ×10)*

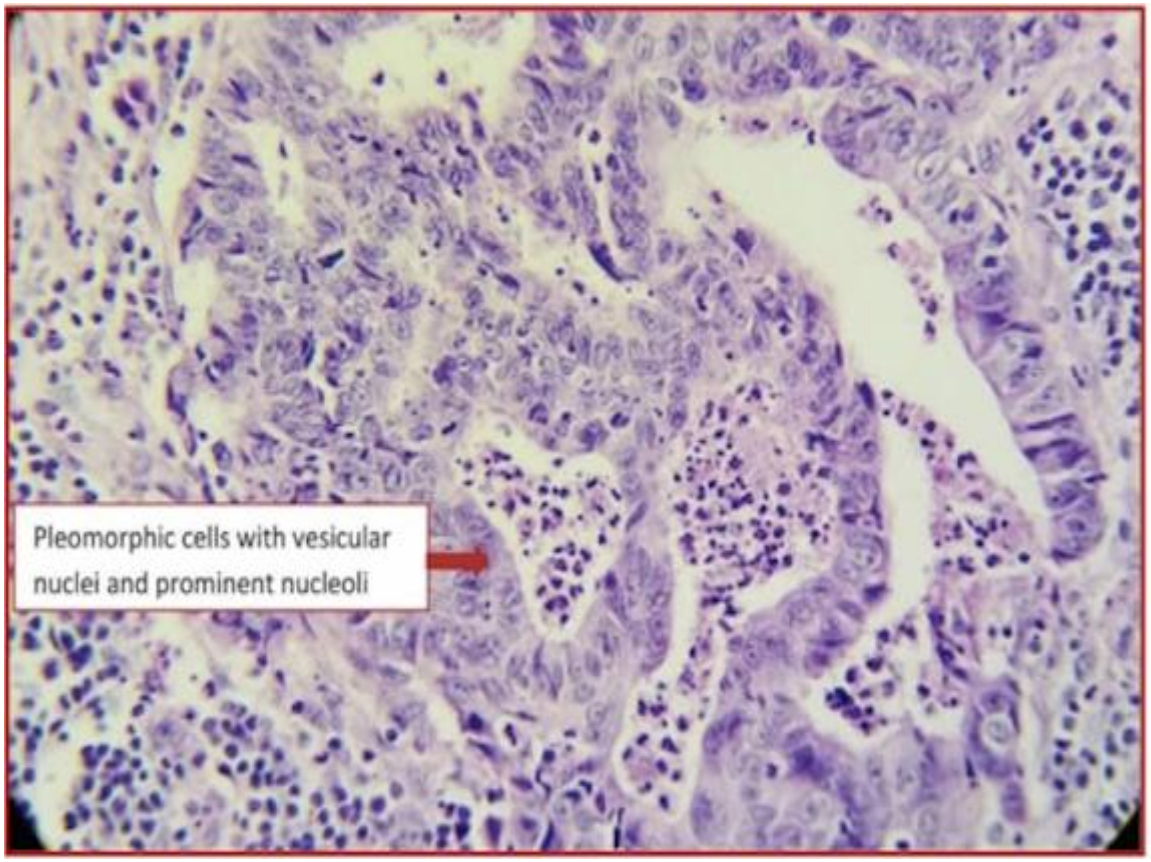


Figure 2. *Histopathological photomicrograph showing metastatic adenocarcinoma of the gallbladder in a lymph node with pleomorphic malignant cells exhibiting vesicular nuclei and prominent nucleoli (H&E stain, ×40).*

Table 3. Gallstone Characteristics

Variable	Frequency
Number of Stones	
Single	58
Multiple	152
Type of Stones	
Cholesterol	10
Mixed	174
Pigment	26

Four cases of acute cholecystitis and four cases of cholesterolosis (1.9% each) were identified. The lesions that were less common included xanthogranulomatous cholecystitis in as much as 2 cases (1.0%) while adenomatous hyperplasia, acalculous cholecystitis, chronic cholecystitis, follicular cholecystitis, hyperplastic polyp with chronic cholecystitis, chronic calculous cholecystitis with choledochal cyst and pseudocyst with chronic calculous cholecystitis occurred in 1 case (0.5%) each.

The characteristics of gallstones were assessed that multiple stones were more common than solitary. A total of 152 cases (72.4%) had multiple gall stones whereas 58 cases (27.6%) had single stones. The most common type of stone in our analysis was mixed stones, which were found in 174 cases. In 26 cases (12.4%), pigment stones were noted, while in 10 cases (4.8%), cholesterol stones were observed.

The predominant lesion seen among all age groups, showing the maximum frequency in the age group of 21-40 years, was Chronic calculous cholecystitis. Statistical analysis revealed a significant relationship between age and histopathological diagnosis ($\chi^2 = 75.86$, $p < 0.001$). Age and number of gallstones were also correlated in our study. All age groups had most patients with multiple stones. However, the association between age and the stone number was not statistically significant ($\chi^2 = 7.687$, $p = 0.053$).

Across all age types, mixed stones type was the highest stone type. However, no association was found between the age of respondents and the type of gallstone ($\chi^2 = 6.425$, $p = 0.377$).

Table 4. Association Between Age Group and Histopathological Diagnosis

Diagnosis	0–20	21–40	41–60	>60
Adenomatous hyperplasia	0	0	0	1
Xanthogranulomatous cholecystitis	0	0	1	1
Acalculous cholecystitis	0	0	0	1
Acute cholecystitis	0	2	1	1
Chronic calculous cholecystitis	4	88	68	25
Chronic calculous cholecystitis with choledochal cyst	1	0	0	0
Cholesterolosis	0	0	1	3

Chronic cholecystitis	0	0	0	1
Hyperplastic polyp with chronic cholecystitis	0	0	1	0
Follicular cholecystitis	0	0	1	0
Malignancy	0	3	3	2
Pseudocyst with chronic calculous cholecystitis	0	1	0	0

In general, the results of the present study showed that gallbladder lesions were mostly seen in middle-aged females, and the most common histopathological diagnosis was chronic calculous cholecystitis. The most common gallstone profile was mixed gallstones. The histopathological diagnosis was significantly associated with age, but no significant association was found between age and number and type of gallstones.

DISCUSSION

The present study evaluated the clinicopathological profile of gall bladder lesions and its association with characteristics of gall stones of 210 cholecystectomy specimens. Gallbladder diseases are one of the most common causes of gastro-intestinal morbidity. Cholelithiasis is one of the commonest causes of cholecystectomy. Histopathological evaluation of resected gallbladders helps understand the range of lesions associated with gallstone disease and allows detection of incidental premalignant and malignant lesions. [1,2,3]

In the current study, predominant cases were found in the age group of 21–40 years followed by the age group of 41–60 years. The results imply that lesions on the gallbladder mainly occur in the third to sixth decade of life. Several studies of gallbladder disease at varied locations have similar age patterns. The enhanced prevalence of gallbladder lesions in middle-aged people can be connected to prolonged exposure to lithogenic factors, changes in bile composition, eating habits, obesity, and inflammatory processes that get established over time. [2,8,10]

In total, 70.95% of the patients were females with a female-to-male ratio of about 2.4:1. These observations are well in line with the established epidemiology of gallstone disease. Hormonal elements are likely believed to contribute significantly to this gender difference. Estrogen contributes to increased cholesterol levels in bile, while progesterone lowers gallbladder motility. It causes bile stasis and promotes gallstone formation. The greater susceptibility of females to gallstone disease and gallbladder pathology may be due to these physiological mechanisms. [2,6,7]

A wide range of gallbladder lesions was revealed by histopathological examination. A diagnosis of chronic calculous cholecystitis was made in 88.1%. Constant mechanical irritation of the mucosa by gallstones, coupled with repeated episodes of inflammation, can give rise to various chronic pathological changes which may consist of fibrosis, mucosal atrophy and infiltration by inflammatory cells. Earlier studies have frequently reported similar findings, where the majority of non-gallbladder cancer cholecystectomy specimens were chronic calculous cholecystitis. [3,4,8,15]

A small number of cases exhibited various types of lesions in the gallbladder. Although they are infrequent, their identification shows the various pathological reactions of the gallbladder to chronic irritation and inflammation. Some lesions like xanthogranulomatous cholecystitis may clinically and radiologically mimic carcinoma, while hyperplastic and proliferative lesions may represent intermediate stages in the spectrum of gallbladder mucosal changes. [15,16,17]

In the present study, the malignant lesions were detected in 3.8% cases, which is an important observation. Gallbladder carcinoma is a rapidly developing cancer that is often diagnosed at an advanced stage because of its lack of symptom specificity. Gallbladder cancer is linked with chronic disease of gallstones (cholelithiasis). Chronic inflammation is thought to induce epithelial dysplasia leading to malignancy. The detection of malignant lesions in routine cholecystectomy specimens highlights the importance of histopathological examination of all resected gallbladders, even when the clinical diagnosis suggests a benign condition. [11,12,14]

The evaluation of gallstone characteristics shows that multiple stones were much more common than solitary stones. In 72.4% of cases, multiple gallstones were found, indicating that gallstone formation is frequently a progressive process

involving repeated precipitation of biliary constituents. Earlier studies have shown similar findings that long-standing lithogenic activity in the gallbladder often results in the formation of multiple calculi. [10,13]
The morphologic analysis of stones showed that mixed stones were the main stone type with 82.9% of cases. There were relatively fewer numbers of pigment stones and cholesterol stones. The high frequency of mixed stones indicates that several factors are probably involved in the formation of gallstones. Cholesterol, bile pigments, calcium salts, infection, inflammation, and other environmental factors are probably responsible for the formation of gallstones. The current study results are similar to many Indian studies, which have reported mixed stones as the most commonly encountered gallstones. [4,16,17,18,20]

In the current study, the relationship between age and histopathological diagnosis was statistically significant. The most common pathological lesion in all age groups was chronic calculous cholecystitis; however, more advanced changes and malignant lesions were seen in older patients. This indicates that continuous exposure to persistent inflammatory stimuli may lead to progressive structural abnormalities within the gallbladder. Mounting inflammation over the years might enhance the chances for complex lesion development and neoplastic change. [11,14,15]

Age and the number of gallstones were not found to be statistically significant. Although most of the cases had multiple stones in all age groups, age by itself does not appear to have a significant effect on the number of stones. Likewise, no significant correlation was observed between age and type of stone. Regardless of age category, mixed stones were the most common stone type. Evidence suggests that other factors such as genetics, diet, metabolism, and bile composition may play a more important role than age in determining gallstone characteristics. [2,6,7]

The present study demonstrates that gallbladder lesions are mainly middle-aged female diseases and closely associated with gallstone disease. The most commonly diagnosed histopathological condition is chronic calculous cholecystitis and the most frequent gallstone profile is multiple mixed gallstones. The important correlation between age and histopathological diagnosis indicates the progressive nature of gallbladder lesions. It is essential to subject all cholecystectomy specimens to routine histopathological examination to identify the full spectrum of gallbladder lesions. Greater insight into the clinicopathological patterns of gallstone disease may aid in achieving early diagnosis, enhance patient management, and prevent disease progression. [3,4,15,16,18]

CONCLUSION

The present study deals with the clinicopathological spectrum of gallbladder lesions and the accompanying gallstone features of 210 cholecystectomy specimens. Most common gall bladder lesions occur in females of middle age. Those are principally present in the age group of 21–40 years. Chronic calculous cholecystitis was the most common histopathological lesion showing gallstone disease and chronic inflammatory changes of gallbladder are closely related. Multiple gallstones were more often encountered than that of solitary stones, while mixed stones were the predominant variety in terms of morphological type. There is a statistically significant association between age and diagnosis. Age influences the pattern of gallbladder pathology. There was no significant relationship between age and the amount/type of gallstones.

The finding of malignant lesions and other rare pathological entities indicates all cholecystectomy specimens, including those performed for a benign condition, should undergo routine histology. The gallbladder lesions along with the characteristics of biliary stones may enhance our understanding of the clinicopathological spectrum of gallbladder disorders. This will help in early diagnosis, suitable management, and preventing disease progression.

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