Original Article

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Pathology Section

Frequency of Preneoplastic and Neoplastic Lesions in Cholecystectomy Specimen from a Tertiary Care Hospital in Uttar Pradesh, India: A Cross-sectional Study

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ABSTRACT

Introduction: Cholelithiasis is known to cause a spectrum of changes, including inflammation in the gallbladder wall, cholesterolosis, atrophy, metaplasia, dysplasia, polyps, and eventually cancer. Gallbladder Carcinoma (GBC) is a rare and highly fatal malignancy.

Aim: To determine the frequency of preneoplastic and neoplastic lesions, along with demographic and clinical aspects of different gallbladder lesions.

Materials and Methods: This cross-sectional study was performed on 788 patients who underwent elective cholecystectomy for gallbladder disease at Hind Medical College, Sitapur, Uttar Pradesh, India, from August 2017 to October 2021. All patients underwent a history and physical examination, followed by routine laboratory tests and other investigations, including full abdominal ultrasound. Histopathologic evaluation of the gallbladder specimen was also performed after surgical resection. Categorical variables were presented as numbers and percentages (%), while continuous variables were presented as mean±Standard Deviation (SD).

Results: A total of 788 cholecystectomy specimens were analysed. The mean age of the patients was 42.49±1.39 years with female predominance 640 (82.05%). The majority of cases were between 40-49 269 (34.13%) and 60-69 399 (50.63) years of age. Preneoplastic changes were found in 764 (96.96%) cases, while neoplastic pathology was evident in 24 (3.04%) cholecystectomy specimens. The most commonly observed preneoplastic change was chronic cholecystitis in 532 (67.54%) cases. Other lesions associated with chronic cholecystitis were cholesterolosis in 76 cases (9.64%), xanthogranulomatous cholecystitis in 34 cases (4.31%), follicular cholecystitis in 30 cases (3.80%), and GBC in 24 cases (3.04%).

Conclusion: This study observed that chronic cholecystitis and cholesterolosis, followed by xanthogranulomatous cholecystitis, were associated with metaplastic changes in gallbladder pathologies. It is believed that metaplasia-dysplasia could be linked to GBC. Therefore, routine microscopic examination is required for all cholecystectomies. However, further studies on gallbladder carcinogenesis are needed.

Keywords: Cholecystectomy, Cholecystitis, Gallbladder carcinoma, Histopathology

INTRODUCTION

Cholecystectomy is one of the most common surgical interventions for benign disease. Gallbladder stones can result in a range of changes, including inflammation in the sac wall, cholesterolosis, atrophy, metaplasia, dysplasia, polyps, and eventually cancer [1]. While cholelithiasis is an important risk factor for gallbladder cancer, only a small proportion of individuals with cholelithiasis develop the disease (1-3%) [2]. Cholelithiasis, which frequently leads to cholecystectomy, can mask other clinical conditions such as benign or malignant neoplasms. The GBC is the most common cancer of the biliary system and the fifth most common gastrointestinal malignancy [3]. Its incidence varies significantly, showing geographic and ethnic variations, with an estimated rate of 10-22 per 100,000 population in northern India [4]. According to GLOBOCAN 2020, the incidence of gallbladder cancer was 97,000 in men and 122,000 in women [5]. The disease is often asymptomatic in the early stages, resulting in diagnosis at an advanced stage. Due to the high-risk of cancer, cholecystectomy is recommended when gallbladder polyps exceed 1cm or when a vascular pedicle is observed on ultrasound. However, imaging techniques have limitations in detecting these polyps, particularly at an early stage, and they are often discovered incidentally through histopathological examination of cholecystectomy specimens. This study aims to determine the frequency of preneoplastic and neoplastic lesions, as well as demographic and clinical characteristics of different gallbladder lesions in the rural population of North Uttar Pradesh, India. Additionally, the study examines various mucosal changes in cholecystectomy specimens.

MATERIALS AND METHODS

A cross-sectional, institution-based study was conducted at the Department of Pathology and Gastro Surgery, Hind Medical College, Sitapur, Uttar Pradesh, India from August 2017 to October 2021. The study was approved from the Institutional Ethics Committee (IEC no. IHEC-HIMSA/MD/MS (20)/RD-08/01-21), a waiver of consent was obtained.

Inclusion criteria: The study included 788 patients who underwent surgery for cholecystitis, cholelithiasis, or both.

Exclusion criteria: Patients with metastatic tumours of the gallbladder and lesions in the bile ducts other than the gallbladder were excluded from the study.

Sample size: Medical records and histopathological findings were retrospectively evaluated for all patients, regardless of sex, age, or race. Postoperative specimens were collected and fixed in 10% formalin, followed by routine histological processing for paraffin embedding. The specimens were then examined after staining with haematoxylin and eosin. Each case was assessed for the presence of gallbladder stones, type of inflammation in the sac wall, cholesterolosis, polyps, metaplasia, dysplasia, cancer, and other lesions. On average, three sections were examined for each cholecystectomy specimen. The histopathology of the cholecystectomy specimens was categorised according to the General World Health Organisation (WHO) classification for gallbladder

and extrahepatic bile ducts [6]. Additionally, clinical symptoms such as hepatomegaly, jaundice, malaise, fever, weight loss, vomiting, nausea, and anorexia were documented.

STATISTICAL ANALYSIS

All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) analysis software version 21.0. Categorical variables were presented as numbers and percentages (%), while continuous variables were presented as mean±SD. The Chi-square test (χ^2) was used to determine the association between clinical and pathological data. A p-value <0.05 was considered significant.

RESULTS

The majority of the cases were female 640 (81.21%), while only 148 (18.79%) were male. There was no significant difference in the mean age between males and females. The mean age of female patients was 41.08±13.02 years, while the mean age of male patients was 43.91±13.76 years [Table/Fig-1]. The highest proportion of cases fell within the age range of 40-49 (269/788, 34.13%) to 60-69 (399/788, 50.63%) years [Table/Fig-2]. Among the 788 cases, chronic cholecystitis was the most frequently observed lesion, present in 532 cases (67.54%) [Table/Fig-3]. The most common symptom associated with gallbladder lesions was pain in the right hypochondrium, present in 71.0% of cases [Table/Fig-4]. Other lesions associated with chronic cholecystitis included cholesterolosis in 76 cases (9.64%), xanthogranulomatous cholecystitis in 34 cases (4.31%), follicular cholecystitis in 30 cases (3.80%), acute on chronic cholecystitis in 24 cases (3.04%), adenomatous hyperplasia in 21 cases (2.66%), and gallbladder cancer in 24 cases (3.04%). Rare lesions found in the study included gallbladder fibrotic changes in 11 cases, cholecystitis with adenomyoma in nine cases, acute cholecystitis in eight cases, Intracholecystic Papillary Tubular Neoplasia (ICPN) in eight cases, intestinal metaplasia in seven cases, gallbladder mucocele in three cases and hyalinising cholecystitis in one case. The histopathological evaluation of cholecystectomy specimens stained with haematoxylin and eosin revealed various preneoplastic and neoplastic changes [Table/Fig-5].

Gender	Total n (%)	Age (years) (Mean±SD)
Female	148 (18.79)	41.08±13.02
Male	640 (81.21)	43.91±13.76
Total	788 (100.0)	42.49±1.39

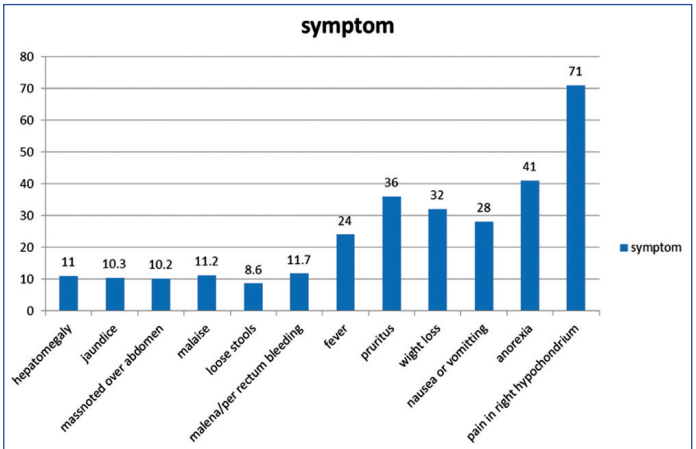
[Table/Fig-1]: Age and gender sex distribution of cases.

Age group (years)	n (%)
40-49	269 (34.13)
50-59	95 (12.05)
60-69	399 (50.63)
70-79	23 (2.91)
80-90	2 (0.25)

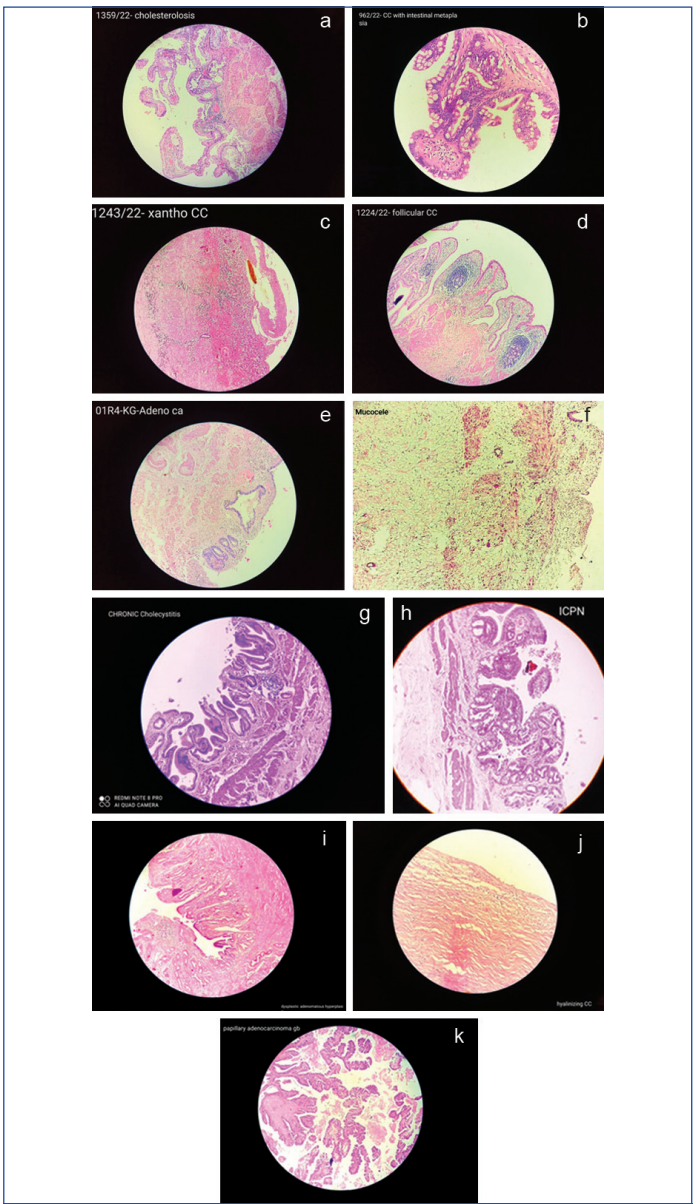
[Table/Fig-2]: Age group distribution of studied patients.

Type of gallbladder lesion		n (%)
Acute cholecystitis		08 (1.01)
Acute on chronic cholecystitis		24 (3.04)
Chronic cholecystitis of usual morphology		532 (67.54)
Chronic cholecystitis other than usual morphology variant	Chronic follicular cholecystitis	30 (3.80)
	Xanthogranulomatous cholecystitis	34 (4.31)
	Adenomatous hyperplasia	21 (2.66)
	Intestinal metaplasia	07 (0.80)
	Cholesterolosis	76 (9.64)
	Cholecystitis with adenomyoma	09 (1.14)
Miscellaneous	Mucocele of GB	03 (0.38)
	Hyalinising cholecystitis	01 (0.23)
	Fibrotic changes in cholecystitis	11 (1.40)
ICPN		08 (1.01)
Neoplasm	Adenocarcinoma	24 (3.04)

[Table/Fig-3]: Histopathological changes of gallbladder.
ICPN: Intracholecystic papillary tubular neoplasia



[Table/Fig-4]: Distribution of symptoms in gallbladder lesions.



[Table/Fig-5]: Histopathological evaluation of Haematoxylin and Eosin-stained cholecystectomy specimens at 10x magnification for: a) Cholesterolosis; b) Cholecystitis with intestinal metaplasia; c) Xanthogranulomatous cholecystitis; d) Follicular cholecystitis; e) Adenocarcinoma; f) Mucocele; g) Chronic cholecystitis; h) Intracholecystic papillary neoplasm; i) Dysplastic adenomatous hyperplasia; j) Hyalinising cholecystitis; k) Papillary adenocarcinoma.

DISCUSSION

Cholecystectomy is a common surgical procedure for the treatment of gallbladder disease. Laparoscopic Cholecystectomy (LC) is the preferred approach due to its advantages such as shorter operative time, lower complication and mortality rates, and faster recovery. However, open cholecystectomy may be necessary in certain cases, such as suspected gallbladder cancer, congenital anomalies of the bile ducts and gallbladder, cirrhosis of the liver, abnormal bleeding, and adhesions between the gallbladder and surrounding tissues. It is recommended to collect an adequate number of samples from cholecystectomy specimens to detect clinically asymptomatic malignancies.

Histopathological examination plays a crucial role in the evaluation of resected gallbladders. While chronic cholecystitis is the most common diagnosis, a wide range of other morphological changes can be observed, including acute cholecystitis, cholesterolosis, xanthogranulomatous cholecystitis, metaplasia, and hyperplasia. Incidental findings such as ICPN and gallbladder cancer can also be encountered. Therefore, precise knowledge and microscopic examination of the gallbladder are necessary to avoid misdiagnosis of these changes as malignant and to ensure that no cases of cancer are overlooked.

In present study, the majority of patients were in the age range of 40 to 60 years, with a mean age of 41.08±13.08 years for females and 43.91±13.76 years for males, respectively. Present study results were consistent with those of Khanna R et al., Tyagi SP et al., and Singh et al., who reported mean ages of 42.5, 43.6, and 45.3, respectively years [7-9]. In present study, 81.21% of the patients were female. Similar results were obtained in the studies by Singh V et al., Mohan H et al., and Bhutra S et al., who reported that 86.97%, 86.54%, and 85% of their patients were female, respectively [10-12]. These age and sex distributions indicate a higher incidence of gallbladder lesions in adult women.

Chronic cholecystitis is the most common gallbladder disease; therefore, most cholecystectomies are performed for this condition [13]. In the present study, chronic cholecystitis was the most common histopathologic finding observed in 67.54% of cases, followed by 9.64% of cholesterolosis cases, 4.31 % of xanthogranulomatous cholecystitis cases, 3.80 % of follicular cholecystitis cases, 3.04% of acute or chronic cholecystitis cases and 1.01% of acute cholecystitis cases. Three cases of gallbladder mucocele and one case of hyalinising cholecystitis. Additionally, hyperplasia (adenomatous type) was found in 2.66% of cases, metaplasia (intestinal type) in 0.80% of cases, IPCN in 1.01% of cases, and gallbladder adenocarcinoma in 3.04% of cases.

Similar findings were reported in a study conducted in Rohtak, Haryana State, India, which found chronic cholecystitis in 45% of cases, acute chronic cholecystitis in 12% of cases, follicular cholecystitis in 5% of cases, xanthogranulomatous cholecystitis in 3% of cases, cholesterolosis in 6% of cases, hyperplasia in 8% of cases, metaplasia in 18% of cases, and carcinoma in 2% of cases among 330 cholecystectomy specimens [14]. Another study by Siddiqui FG et al., reported chronic cholecystitis in 92.3% of cases, acute chronic cholecystitis in 4.5% of cases, and adenocarcinoma in 2.7% of cases among 220 cholecystectomy specimens [15].

Intraepithelial neoplasia, known as IPCN when found in the gallbladder, is a rare tumor that resembles Intraductal Papillary Neoplasms (IPNs) and Tubulopapillary Neoplasms (ITPNs) found in the pancreas [16]. In 2019, the WHO recognised these lesions as a distinct entity under the name ICPNs. ICPN shows intraluminal papillae growth that may be associated with invasive carcinoma. Patients with ICPN clinically resemble those with cholelithiasis, cholangiocarcinoma, and gallbladder cancer [17]. They are more common in women in the 26-65 age groups. In present study, eight cases (1.01%) of ICPNs were found, predominantly in females. ICPNs account for only 6.5% of all surgically resected gallbladder cancers.

Gallbladder cancer is a rare but deadly disease. In present study, 24 cases (3.04%) of gallbladder cancer were observed. Different studies have reported different incidences ranging from 1% to 12.4%. Terada T found an incidence of malignancy of 2.2% in their study, while Ghimire P et al., found a rate of 1.28% in another study [18-20]. This difference was due to the fact that gallbladder cancer usually shows up late in the advanced stage. Clinically, a significant proportion of gallbladder malignancies is asymptomatic and is found incidentally on histopathological examination [21]. In the present study, the most common symptom of gallbladder cancer in present study was pain in the right hypochondrium, followed by anorexia, itching, weight loss, nausea, and vomiting. In the study from Nepal, in which 47 patients with gallbladder cancer took part, abdominal pain was reported as the main symptom [22]. It has been reported that factors such as Asian, African or American race, age over 60 years, female gender, obesity, gallstones, polypoid lesions, high Alkaline Phosphatase (ALP) levels and diet can cause a high prevalence of gallbladder disease [23]. Prolonged exposure to female sex hormones can increase the risk of gallbladder cancer [24]. Gallbladder stones can lead to chronic inflammation, mucosal dysplasia, and eventually the development of cancer. Diagnosis of gallbladder cancer can be challenging as both cholecystitis and cancer can cause thickening of the gallbladder wall. Therefore, histopathological examination is essential to confirm the diagnosis in any resected cholecystectomy specimen.

Limitation(s)

The present study had a limitation regarding the follow-up of cases with preneoplastic changes. Future studies should consider incorporating follow-up data for a more comprehensive analysis.

CONCLUSION(S)

Chronic cholecystitis was the most common histomorphological feature observed. Additionally, a range of other findings such as cholesterolosis and xanthogranulomatous cholecystitis were also observed. Cholelithiasis and cholecystitis can lead to various pathological mucosal changes that serve as precursors to carcinoma. Antral metaplasia and intestinal metaplasia are considered precursors to dysplasia in the gallbladder. Screening for premalignant lesions is crucial in order to reduce mortality and morbidity in high-risk patients. Timely intervention is vital for curative treatment and long-term patient survival. Therefore, histopathological examination should be performed in every cholecystectomy case to detect metaplasia, dysplasia, or carcinoma.

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