



**Spectrum of lesions on routine histopathological examination of gallbladder specimens following cholecystectomy:
A 2-year study in a tertiary care hospital**

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Abstract

Background: Laparoscopic cholecystectomy is considered to be the gold standard for symptomatic gallstones. As a routine standard practice, it is made compulsory for practitioners to submit all gallbladders removed surgically to be sent for histopathology to exclude any gallbladder pathologies that can significantly impact the management of patients like gallbladder malignancies. The aim of the study is to analyze the spectrum of diseases found on routine histopathological examination of gallbladder specimens submitted after laparoscopic cholecystectomy in a tertiary care hospital.

Method: This is a two-year retrospective study where histopathology reports of gallbladder specimens, were

retrieved from the Pathology database from July 2021 to June 2023. The demographic, clinical details, and histopathological features of these cases were studied and analyzed.

Results: Of the Two hundred and sixty patients included, 194 were females and 66 were males, with the mean age of 40. Common presenting symptoms were pain in the upper abdomen followed by dyspepsia. The most common histopathological findings were chronic cholecystitis and Pyloric/Intestinal metaplasia, observed in 56% and 16% of the patients, respectively. While only three cases of gallbladder adenocarcinoma were observed, multiple specimens were labeled as

pre-malignant lesions including reactive atypia and intestinal metaplasia.

Conclusion: GB disease remains a major indication for cholecystectomy. Postoperative histopathological evaluation of the excised GB specimens divulges a vast spectrum of underlying pathologies. Of these, chronic cholecystitis, cholesterolosis, and acute-on-chronic cholecystitis remain the most prevalent. GB can be considered as a hidden grave for pre-malignant and malignant lesions and therefore, all cholecystectomy specimens should be thoroughly sampled and examined on microscopy for occult malignancies. Left undetected, these lesions can progress to GB adenocarcinoma, which is noted to have a particularly forbidding prognosis.

Keywords: Laparoscopic, cholecystectomy, Pyloric/Intestinal metaplasia.

Introduction

Cholecystectomy is among the most common worldwide abdominal surgical procedures (1). It is the standard protocol to send all GB specimens for routine histopathological examination (HPE) postoperatively, regardless of any clinical and radiological findings, to exclude unexpected gallbladder cancer (GBC) (2). GBC is very rare with a bad prognosis (3). The incidental finding of GBC in these specimens is around 0.5–1.1%. Gallstone has always been considered an important risk factor for GBC however this causal relationship has yet to be established. Most commonly, cholelithiasis produces a series of epithelial pathological changes which could be precursor lesions of gallbladder cancer in the background of inflammation. These changes include hyperplasia, dysplasia, and metaplasia. Gallbladder dysplasia (GBD) and adenoma are pre-malignant lesions, which may progress to carcinoma through different pathways. (4,5) Gall bladder (GB) neoplasms are relatively uncommon and are usually asymptomatic

during early stages. (5). We analyzed the clinicopathological spectrum of lesions in routine histopathological examination of cholecystectomy specimens.

Material & methods

A retrospective study was done on all patients who underwent cholecystectomy with or without gallstone disease over two years from July 2021 to June 2023. The hospital records of patients were retrieved and reviewed: demographic data, and preoperative clinical findings. Macroscopic appearance and histopathological findings were also recorded. The gall bladder wall was considered to be thickened if ≥ 3 mm on preoperative imaging or surgeon's comment (on operative findings) and histopathology report. The normal thickness of the gall bladder wall is reported to be 1-2 mm. AJCC TNM system was used to stage gallbladder cancer. Data was entered and analyzed using SPSS 20.0

Result

Two hundred and sixty patients underwent cholecystectomy during the study period. Most of them were females 74.6 % (194). The average age of patients was 40 years (range 20– 78 years) as shown in Table 1. Common presenting symptoms were pain in the upper abdomen followed by dyspepsia as shown in Table 3

Table 1: Demographic Features Showing Frequency of Age

Age Groups (Years)	Frequency	Percentage (%)
5-25	27	10.3
26-45	120	46.1
46-65	56	21.5
66-75	51	19.6
>75	06	23

Table 2: Demographic Features showing the distribution of Sex of Patients

Gender	Frequency	Percentage (%)
Male	66	25.4
Female	194	74.6

Table 3: Common presenting symptoms

Symptoms	Number of Patients	Percentage (%)
Nausea/vomiting	35	13.4
Pain in the upper abdomen	160	61.5
Intolerance to food	39	15
Tenderness Rt Hypochondrium	26	10

Two hundred and sixty patient histopathological data were collected. Chronic cholecystitis with Cholelithiasis was found to be more common and seen in 146(56%) patients followed by Chronic Cholecystitis with Pyloric/Intestinal metaplasia seen in 42(16%) cases, and cholesterolosis in 31(11.9%) cases respectively. Acute cholecystitis was seen in 18 (6.9%) cases and Adenoma/Dysplasia was found in 8(3%) patients. Three cases each of xanthogranulomatous cholecystitis, eosinophilic cholecystitis, and Gallbladder Polyp were found. Incidentally, gall bladder cancer was found in 3(1.1%) patients as shown in Table 4.

Table 4: Details of histopathological findings from 260 cholecystectomy specimen

Histopathological Diagnosis	Number of Patients	Percentage (%)
Chronic cholecystitis (CC) with cholelithiasis	146	56.1
Acute cholecystitis	18	6.9
Xanthogranulomatous cholecystitis (XGC)	03	1.1
Eosinopphiic Cholecystitis	03	1.1
Adenomyomatosis	02	0.7
CC with Cholesterolosis	31	11.9
Empyema gallbladder	01	0.3
Gallbladder polyp	03	1.1
CC with Pyloric/Intestinal metaplasia	42	16
Gallbladder adenoma/Dysplasia	08	03
Carcinoma	03	1.1
Total	260	100

Out of 03 cases diagnosed with incidentally having gall bladder carcinoma, one was male and two were female patients. The mean age of patients was 59.6 (range 43-72 years). The thickened gall bladder was found in 2 (56.6%) of patients in the preoperative imaging study. All patients underwent laparoscopic cholecystectomy but 1/3 converted to open because of dense adhesions or difficulty in defining Calot’s triangle. Macroscopic abnormal appearance was found in all of these cases presented with nonspecific signs and symptoms. Nodularity/polypoid projections were present in one case and all three patients had macroscopic appearance of thickened gall bladder wall and gall stones. Details of each case are shown in Table 3.

Most of the cases were T1 and T2 on TNM staging. None of the patients with normal morphology and macroscopic appearance had gall bladder malignancy.

Table 5. Details of the patients with a histopathological diagnosis of gallbladder carcinoma

Patient	Age (Years)	Sex	Preoperative Suspicion	Intraoperative Finding	Type of Malignancy
1.	43	F	No	Thick-walled gallbladder, severe inflammation, Gall stones	Well-differentiated Adenocarcinoma
2.	64	F	no	Thick-walled gallbladder, severe inflammation, severe adhesions, Gall stones	Signet ring cell Adenocarcinoma
3.	72	M	Yes	Gallbladder nodule/polypoid, severe inflammation, Gall stones severe adhesions.	Poorly differentiated Adenocarcinoma

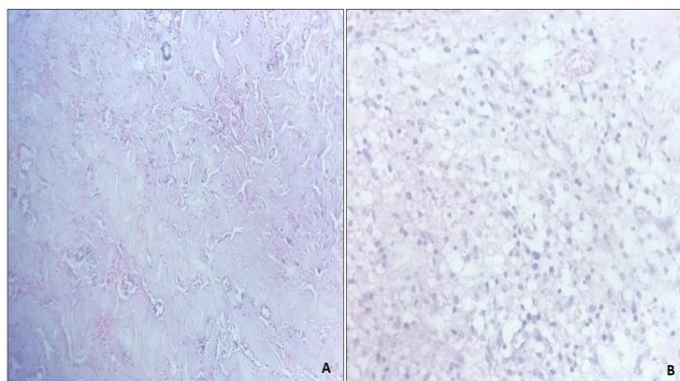


Figure 1A-B: A- Extensive hyalinization noted in Hyalinizing cholecystitis [H&E- 40X]; B- Sheets of histiocytes noted in Xantho-granulomatous cholecystitis [H&E- 40X].

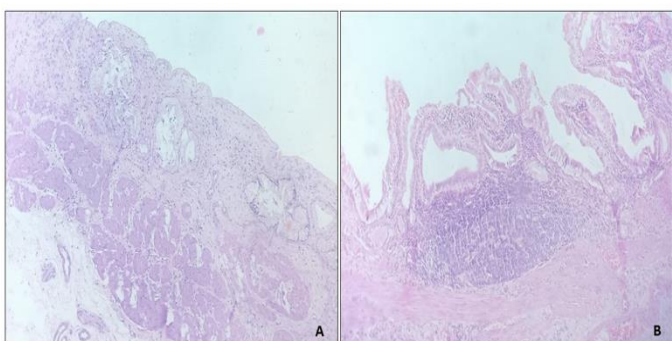


Figure 2A-B: A- Intestinal metaplasia noted in lamina propria [H&E- 20X]; B- Lymphoid follicles noted in lamina propria in case of Follicular cholecystitis [H&E- 20X]

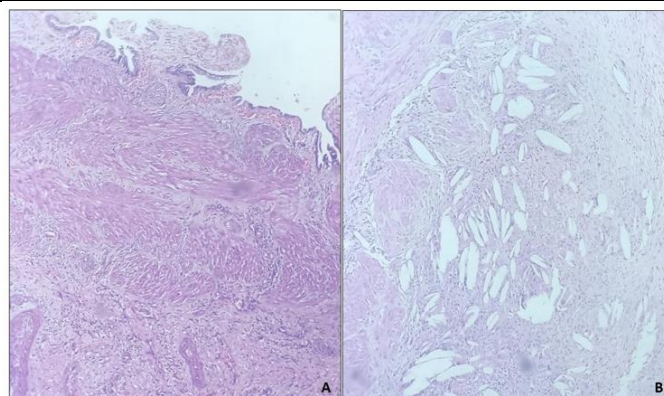


Figure 3A-B: A- Hypertrophy of muscle is noted reaching upto epithelial layer [H&E- 20X]; B- Cholesterol clefts noted in section of gall bladder [H&E- 20X].

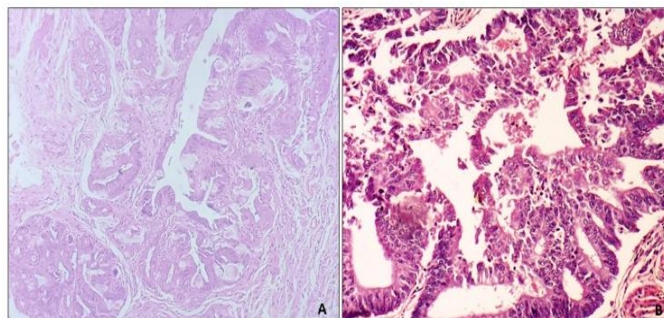


Figure 4A-B: A- High grade dysplasia noted in focal area in lamina propria [H&E- 20X]; B- Adenocarcinoma gall bladder with patchy necrosis [H&E- 40X]

Discussion

Diseases of the gallbladder often mandate prompt surgical intervention. Of these, chronic cholecystitis, which is an established risk factor for gallbladder carcinoma, is exceedingly common. The employment of histopathological techniques remains imperative in the detection of premalignant and malignant lesions of Gall bladder (6). Cancer of gall bladder usually manifests itself in advance stages and carries a poor prognosis. It is most common malignancy of extra-hepatic biliary system [7]. Treatment of gall bladder malignancy depends on stage of disease with which patient presents.

In the present study, a female predominance amongst the patient population was observed. In concert with this finding, a study conducted in India, a neighbouring nation, concluded a male-to-female ratio of 1:2.4 [8,9]. Interestingly, the female gender is noted to be a risk factor that predisposes to the development of gallstones. Almost all of the patients in our study presented with cholelithiasis, which can eventually herald the onset of various pathologies, such as acute cholecystitis, chronic cholecystitis, follicular cholecystitis, and cholesterolosis. The prevalence of chronic cholecystitis, the most common pathology within our patient population, was noted to be 84.2%. In accordance with this finding, a study concluded the prevalence of chronic cholecystitis to be 79.8%, which bears remarkable resemblance to our finding [10].

Cholesterolosis results from mucosal villous hypertrophy and a resultant accumulation of cholesterol esters and triglycerides in a diffuse or polypoid form in the macrophages present within the wall of the GB. In our study, cholesterolosis was observed in 11.9% of the cases along with chronic cholecystitis. A study conducted by Sangwan et al. reported a prevalence of 9.43% [10]. The prevalence of the pathology in our study was therefore

noted to be significantly higher and along with feature of chronic cholecystitis.

Pyloric /Intestinal metaplasia and Gall bladder adenoma/ Dysplasia were observed in 03% and 16% of the cases, respectively. While their prevalence in the current study was fairly high, their malignant potential should be kept in mind. Intestinal metaplasia and Dysplasia are both premalignant conditions that can eventually lead to the development of carcinoma. High grade dysplasia is reported in 1 to 3.5% of cholecystectomies performed and low-grade dysplasia in up to 15% of areas of the world with high incidence of GBC. (11) Also, most of the patients who presented with these premalignant afflictions belonged to the older age groups. This indicates that an increased age at presentation increases the risk of a malignant transformation [12,13]. If not detected early, these lesions can orchestrate the pathogenesis that underlies the development of GBC. It is therefore necessary to evaluate the histopathology of each GB specimen, irrespective of its macroscopic appearance intraoperatively. Doing so can aid the early detection of carcinoma in high-risk patients, thus curbing the risk of progression to advanced disease.

XGC, a chronic, focal, or diffuse fibroinflammatory process resulting from an intramural accumulation of foamy histiocytes, was observed in 1% of the cases. XGC mimics GB malignancy. Moreover, its association with GBC has also been well-established [10]

GB [14]. In this study, empyema of the GB was observed in .01% of the cases, which is very low compared to a prevalence rate of 0.71% as seen in another study [15]

Gallstone has always been considered an important risk factor for GBC however this causal relationship has yet to be established. In our study, 90% of cases of GBC had associated gallstones, as observed by other authors. (16-18) Bhawna et al in their study have also illustrated that

GB dysplasia, tubular adenomas, carcinoma in situ, and invasive carcinoma were frequently associated with gallstones. Similarly, Gupta et al. (19) also found a high prevalence of gallstones in all GB lesions.

GB adenocarcinoma was observed in merely 1% of the cases. Various studies have reported prevalence rates ranging from 0.5% to 1.05% of the total cases [19,20]. Despite the advent of modern diagnostic techniques, GBC is still diagnosed at a late stage and is thus associated with a poor prognosis [20]. Furthermore, since GBC often remains clinically silent in its initial stages, it evades prompt detection.

At present, simple cholecystectomy is considered an adequate therapy for early GBC, and radical operation should be carried out in the advanced stage of the disease to improve the prognosis of patients. (21) As a standard protocol, in all cases of adenoma, dysplasia, and GBC simple cholecystectomy is performed. It has been documented that incidentally detected GBCs are surgically resectable with good overall survival. (22,23)

Conclusion

Detection of gallbladder lesions in routine cholecystectomy specimens, in the absence of clinical-radiological suspicion, emphasizes the importance of a careful histopathological examination of all cholecystectomy specimens. Postoperative histopathological evaluation of the excised GB specimens reveals a vast spectrum of underlying pathologies. Of these, chronic cholecystitis, cholesterolosis, and acute cholecystitis remain the most prevalent. The observation of histopathological features reveals a relationship between gall stones and premalignant and malignant conditions of GB. Since metaplasia and dysplasia are known precursor lesions for invasive carcinomas, vigilant microscopic examination is

warranted to enable early diagnosis and prompt treatment.

Take Home Message

1. Gallbladder can be considered as hidden graves for premalignant and malignant lesions. Therefore, all cholecystectomy specimens should be thoroughly sampled for occult malignancies.
2. Since adenomas and dysplasias are known precursor lesions for invasive carcinomas, a vigilant microscopic examination is warranted to enable early diagnosis and prompt treatment.
3. Morphological examination reveals the relationship between gallstone and gallbladder lesions.

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