

Histopathological Spectrum of Gallbladder Lesions and Outcome Of Routine Histopathological Examination Of Cholecystectomy Specimens

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Abstract

Background: Cholecystectomy specimens are very frequently examined in a surgical pathology practice and reveal a myriad of lesions. Cholelithiasis is a major risk factor for most of the gallbladder diseases. Gallbladder is one of the most common organs where the incidental carcinoma is commonly reported in published literature. This study was intended to evaluate the histopathological spectrum of gallbladder lesions and to assess the utility of histopathological examination of cholecystectomy specimens to diagnose the incidental carcinoma. **Materials and Methods:** This observational and descriptive study was carried out on a total 400 cholecystectomy specimens by conventional histopathological methods. **Results:** Cholecystectomy specimens comprised of 4.70% all surgical pathology specimens. The mean age of patients was 41.84 ± 13.74 years. A striking female preponderance (F: M = 3.49:1) was noted. Most cases were associated with gallstones (83.5%). Non-neoplastic and neoplastic lesions comprised 97.5%, and 2.5% respectively. Chronic cholecystitis was the most frequent pathology (67.5%). Adenocarcinoma was observed in 2.25% cases and 88.89% of all malignant lesions were reported as an incidental finding. **Conclusion:** Gallstones are consistently observed in both neoplastic as well as non-neoplastic lesions of gallbladder. Many premalignant and malignant lesions may masquerade as chronic cholecystitis; both on clinical and radiological parameters and so, histopathology proves to be a gold standard tool for the correct diagnosis. This study affirms the importance of routine histopathological examination of each and every cholecystectomy specimen; as incidental detection of gallbladder carcinoma is very high.

Key words: Histopathology, Cholecystectomy, Gallstones, Cholecystitis, Adenocarcinoma

Introduction

Cholecystectomy is one of the most common abdominal surgical procedures performed worldwide. Most of the cholecystectomy procedures are performed in patients with gallstone disease associated with its relevant symptoms or complications. The vast majority of gallstones are “silent.” About 10–15% of the adult western population develop gallstones, with 1–4% a year develop symptoms¹. In an Asian population, the prevalence of gallstones is around 3–5%². The gallbladder is subjected to a varied spectrum of diseases; including congenital anomalies, inflammatory processes, and tumours with tumour-like conditions. The association of cholelithiasis with both inflammatory and neoplastic lesions has been proven.

The symptomatology associated with gallbladder cancer usually mimics that of chronic cholecystitis, and thus, many cancers are detected incidentally and as advanced stage tumours in cholecystectomy

specimens with no clinical suspicion of malignancy. Incidental gallbladder carcinoma (GBC) is found in 0.2%-2.9% of all cholecystectomies performed for gallstone disease³. The incidence of GBC varies widely among different geographical regions and ethnic groups. Northern India and Pakistan, East Asia, South America, and Eastern Europe are found to have the highest rates of GBC⁴.

This study was intended to evaluate the histopathological spectrum of gallbladder lesions to estimate the relative frequency of various lesions; and to establish the utility of routine histopathological examination to pick up the incidental cancers in cholecystectomy specimens.

Materials and Methods

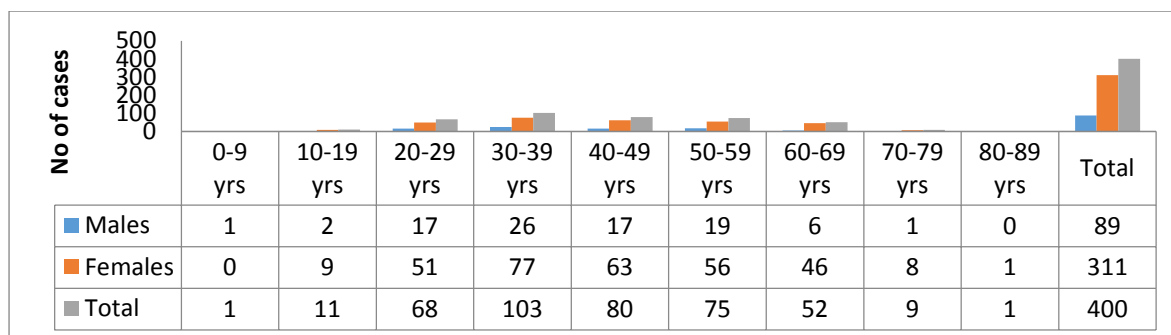
This observational and descriptive study was carried out on a total 400 cholecystectomy specimens received in the Department of Pathology, at a tertiary care hospital affiliated to medical college, Ahmedabad during the period of two years; from June -2016 to May - 2018. All cholecystectomy specimens, including laprotomy and laproscopic resection specimens were included in the study sample; while the specimens with inadequate clinical and demographic details or autolyzed specimens were excluded. A thorough gross examination was carried out. After formalin fixation, representative tissue sections were taken and processed by routine paraffin embedding technique. A 4-5 micron thick tissue sections were cut and stained by routine Hematoxylin and Eosin (H & E) stain. Microscopic examination was done and a histopathological diagnosis was rendered. Gallbladder carcinoma staging was done by American Joint Committee recommendations for cancer staging (AJCC). Demographic and clinical data were obtained from the histopathology requisition forms or from the patients' case sheets. Data were statistically analyzed using Microsoft Excel and Graphpad software. The demographic profile of the patients and histopathological findings were summarized in proportion (%), ratio, mean (\pm standard deviation), median and range. Appropriate tests of statistical significance (Chi square test, Fisher exact test and Student's t test) were applied.

Ethical approval: The study proposal was approved by the institutional review board committee.

Results

The cholecystectomy specimens comprised 400 specimens (4.70%) out of total 8500 surgical pathology specimens received during the study period. Of all the patients, 311(77.75%) were female and 89 (22.25%) were male, with a female to male ratio of 3.49:1(Fig-1). The gender difference was found to be highly significant statistically ($p < 0.0001$). The age of the patients ranged from 8 to 81 years; with mean and median age of the patients being 41.84 ± 13.74 years (95% CI= 40.49-43.19 yrs) and 40 years respectively. Majority of patients were reported between 3rd to 7th decades with maximum number of cases in 4th decade. Patients with non-neoplastic gallbladder diseases showed a wide age distribution; whereas all neoplastic lesions were seen after 4th decade. The mean age of patients with non-neoplastic and neoplastic lesions was 41.46 ± 13.66 years (median age 40 years, 95% CI= 40.10-42.81 yrs) and 57 ± 7.04 years (median age 60 years, 95% CI= 52.64-61.36 yrs) respectively. The difference in age of patients between non-neoplastic and neoplastic group of lesions was found to be statistically highly significant ($p = 0.0004$).

Fig-1: Age and sex distribution of patients with cholecystectomy specimens



Right upper quadrant abdominal pain was the most common presenting symptom. Other symptoms were: anorexia, nausea, vomiting, dyspepsia, belching, bloating, jaundice etc. in varying frequencies and combination.

Table-1: Histopathological spectrum of gallbladder lesions and their association with gallstones

Category of lesion	Histopathology diagnosis	No. (%)	Gall stones present No. (%)	Gall Stones absent No. (%)
Non-neoplastic N=390 (97.5%)	Chronic cholecystitis	270 (67.5)	220 (55)	50 (12.5)
	Acute cholecystitis	96 (24)	83 (20.75)	13 (3.25)
	Empyema	2 (0.5)	2 (0.5)	0 (0)
	Cholesterosis	10 (2.5)	10 (2.5)	0 (0)
	Xanthogranulomatous cholecystitis	4 (1)	4 (1)	0 (0)
	Lympho eosinophilic cholecystitis	1(0.25)	0 (0)	1(0.25)
	Follicular cholecystitis	1(0.25)	1 (0.25)	0 (0)
	Adenomyoma	3 (0.75)	2 (0.5)	1(0.25)
	Metaplasia	3 (0.75)	2 (0.5)	1(0.25)
Neoplastic N=10 (2.5%)	Flat (nontumoral) dysplasia	1 (0.25)	1(0.25)	0 (0)
	Adenocarcinoma	9 (2.25)	9 (2.25)	0 (0)
Total		400 (100)	334 (83.5)	66 (16.5)

The histopathological diagnosis with a frequency of gallstones in different entities is depicted in Table -1. On gross examination, gallstones were present in 334 (83.5%) specimens. Non-neoplastic gallbladder lesions comprised 97.5%; with only 2.5% being the neoplastic lesions. Among the non-neoplastic lesions, chronic cholecystitis was found to be the most frequent pathology (67.5%); which was followed by acute cholecystitis (24%) and cholesterosis (2.5%). Special morphologic variants of chronic cholecystitis reported were; xanthogranulomatous cholecystitis, follicular cholecystitis and lympho eosinophilic cholecystitis. Two cases were diagnosed as empyema of gallbladder and three cases as adenomyoma. Out of three cases of metaplasia, two showed the features of intestinal metaplasia; while one showed the pyloric gland metaplasia. In all cases of adenomyoma and metaplasia; associated features of chronic cholecystitis were present.

In the category of neoplastic lesions, one case was diagnosed as premalignant lesion; flat (nontumoral) dysplasia and 9 cases showed features of adenocarcinoma. Flat (nontumoral) dysplasia did not show any gross abnormality in the cholecystectomy specimen. Microscopically, it showed high grade dysplasia with intestinal metaplasia. Extensive sampling of the specimen by Swiss roll method was performed to rule out any focus of invasive carcinoma. Amongst all adenocarcinomas, the most common histopathological type observed was pancreaticobiliary type (7/9 cases, 77.78%); followed by one case each (1/9 cases, 11.11%) of intestinal and mucinous adenocarcinoma. Perineural invasion was observed in all cases of adenocarcinoma except in mucinous type. Seven cases of adenocarcinoma (7/9 cases, 77.78%) were moderately differentiated (Grade-2) and two cases (2/9 cases, 22.22%) were poorly differentiated (Grade-3). Five cases (5/9 cases, 55.56 %) were assigned to stage pT2, three cases (3/9 cases, 33.33%) to stage pT1b and one case (1/9 case, 11.11%) to stage pT3. We could assign the stage only by tumour extension (pT status). Lymphnode status (pN) or distant metastasis (pM) could not be assessed for any malignant tumour. Gallbladder adenocarcinomas were incidental findings in the majority of cases (8/9 cases, 88.89%) without any clinical or radiological suspicion of malignancy. All these cases did not reveal any gross mass lesion except diffuse thickening of the wall. Only one case (1/9 cases, 11.11%) was preoperatively diagnosed as a malignant lesion on clinico-radiological ground; which had a typical nodular mass projecting into the lumen of the gallbladder. Gallstones were present in all malignant and premalignant lesions. However, the difference of gallstone association between the neoplastic and non-neoplastic group of lesions was not observed to be statistically significant ($p=0.1938$; p value > 0.05).

DISCUSSION:

Gallbladder diseases are common ailments encountered in surgical pathology practice. Many literatures reviewed indicate that, the gallbladder diseases are more common in female as compared to male. In the present study, female to male ratio of 3.49:1 was observed. This finding is in concordance with the study

done by Dincel O et al⁵, Ashesh Kumar Jha et al⁶ and Talal Almas et al⁷; which showed female to male ratio of 3.7: 1, 3.23:1 and 2.95: 1 respectively. This female preponderance is typically associated with increased risk of gallstones development in female as compared to male; which serves as a main culprit for subsequent gallbladder diseases. In the Western societies, about 80 % of the gallstones are composed primarily of cholesterol. Female sex hormones are most likely to be responsible for the increased risk of gallstones in female. Estrogen increases biliary cholesterol secretion causing cholesterol supersaturation of bile. Thus, hormone replacement therapy in postmenopausal women and oral contraceptives have also been described to be associated with an increased risk for gallstone disease. Pregnancy is also a major risk factor for gallstone formation⁸.

Majority of cases were noted in 4th decade in the present study with mean age of patients being 41.84 ± 13.74 years. The mean age of patients with gallbladder diseases reported in different series was 47.5 ± 14.3 years⁵, 43.10 ± 13.90 years⁶, 45.77±14.65 years⁷ and 41.30 ± 8.43 years⁹; which coincides with the age distribution of patients in our study. The mean age of patients with malignant gallbladder lesions in the present study was 57 years. This was reported to be 65.6 years and 49 years respectively in the study of Dincel O et al⁵ and Ashesh Kumar Jha et al⁶. In many other studies, gallbladder carcinoma was commonly observed after 4th decade^{10, 11}.

Cholelithiasis constitutes the most prevalent biliary tract pathology globally with its prevalence rate in adults in developed countries is 10%-15%¹². Gallstones are a major cause of morbidity and mortality throughout the world. They are intricately associated with various lesions like acute cholecystitis, chronic cholecystitis along with its variants and gallbladder carcinoma. In the present study, 83.5% cases (334/400 cases) had gallstones. This is in accordance with the study of Savita Agarwal et al¹¹ and Selvi et al¹³; which reported 95.98 % and 83.3% of patients with gallstones in their studies. It is widely reported that long standing mucosal irritation by the stones cause atypical cellular changes and increased cellular proliferation. It has been hypothesized that in longstanding cases, these areas of hyperplasia progress to metaplasia and carcinoma-in- situ¹⁴.

Table-2 Histopathological analysis of gallbladder lesions in different studies

Histopathological Diagnosis	Present study	Talal Almas ⁷	Savita et al ¹¹	Cyrus Dara Jokhi et al ¹⁵	Sabina Khan et al ¹⁶	Shaffy Thukral et al ¹⁷	Arathi et al ¹⁸	Devi et al ¹⁹
Chronic cholecystitis	67.5	78.7	69.1	82.3	77.7	54.6	86.3	82
Acute cholecystitis / Acute on chronic cholecystitis / Gangrenous cholecystitis	24	18.8	11.5	10	2.7	0.71	8.4	13.5
Empyema	0.5	1.1	0.35	-	0.5	0.71	-	0.5
Cholesterosis	2.5	32.8	18.2	-	10	22.69	2.9	2.5
Xanthogranulomatous cholecystitis	1	1.1	2.1	2.3	3.6	0.71	1.8	1
Lymphoeosinophilic cholecystitis/ Eosinophilic cholecystitis	0.25	0.2	0.82	0.8	0.5	0.71	-	-
Follicular cholecystitis	0.25	0.5	2.4	0.8	0.25	-	-	-
Adenomyoma / Adenomyomatosis	0.75	-	5.2	0.8	0.5	-	-	-
Metaplasia	0.75	0.2	25.9	-	1	3.54	-	-
Dysplasia / adenoma	0.25	-	1.7	-	-	-	-	-
Adenocarcinoma / Other malignant tumours	2.25	0.2	0.94	3	2.2	4.95	1.6	0.5

Comparative analysis of various gallbladder lesions diagnosed histopathologically in different studies is presented in Table-2. Chronic cholecystitis is the universally observed predominant lesion in many studies including ours. Acute cholecystitis and its variants viz. empyema and gangrenous cholecystitis are less common than its chronic counterpart in most series. Another fairly common lesion observed is

cholesterosis. Its prevalence varies between 9% and 26%²⁰. Adenomyoma (when focal or segmental) or adenomyomatosis (when diffuse) are misnomers (tumour like conditions) and they represent an exaggerated extension of Rokitansky-Aschoff sinuses, within hypertrophic smooth muscle. Rokitansky-Aschoff sinuses may sometimes simulate malignancy particularly in instances; when they are associated with reactive atypia, dysplasia or mucin spills in stroma due to rupture. This problem is sometimes compounded by close approximation of nerves surrounding the dilated glands, creating a false impression of intraneural and perineural invasion. In our opinion, the architecture of lesion serves as an important indicator to distinguish such mimickers of malignancy from true malignant lesions.

In the neoplastic category, one case was diagnosed as a premalignant lesion (Flat-non tumoral dysplasia) in the present study. Recently, the noninvasive (pre-malignant) neoplastic lesions that form masses in the gallbladder have been grouped under the category of intracholecystic papillary-tubular neoplasms (ICPNs); and those without any apparent mass forming lesions have been placed under the category of flat / nontumoral preinvasive lesions. The flat (nontumoral) dysplasia is difficult to see grossly and is often an incidental finding in cholecystectomy specimens. Flat dysplasia can consist of biliary, intestinal, or foveolar cell types and is graded as low- or high-grade/carcinoma in situ. If flat dysplasia is detected in initial sections of a gallbladder, the remainder should be extensively sampled to exclude an adjacent adenocarcinoma²¹. Grossly, gallbladder carcinoma may present as a diffusely growing (70%) or nodular, polypoid, or papillary mass (30%)^{22,23}. In this study, only intestinal type of adenocarcinoma had a nodular mass lesion and it was the only case which could be diagnosed as a malignant lesion preoperatively by imaging study. The pancreaticobiliary type of adenocarcinoma is the most common histologic type of gallbladder carcinoma. Perineural invasion is a common feature with gallbladder carcinoma and it was observed in all cases except in a mucinous carcinoma in this study. Mucinous adenocarcinomas are typically presented at an advanced stage and have a poor prognosis. In this study, mucinous carcinoma was assigned to stage pT3 due to direct invasion of liver tissue.

Table-3: Frequency of incidental carcinoma of gallbladder reported in various studies

Incidental gallbladder carcinoma	Present study	Dincel, et al5	Jha, et al6	Savita et al11	Cyrus Dara Jokhi et al15	Sabina Khan et al16	Yadav R et al24
As a percentage among all gallbladder lesions	2	04	1.85	0.7	1.5	4.45	1.26
As a percentage among all malignant tumours of gallbladder	88.89	100	100	75	50	100	100

In the present study, almost all cases of adenocarcinoma (8/9, 88.89 %) were diagnosed incidentally; in which there was no clinical and/or radiological suspicion of malignancy. Many studies depicted high rate of incidental detection of gallbladder carcinomas (Table-3). This is because of the fact that, many gallbladders with carcinomas usually also contain calculi (80% -90% of the cases) and exhibit marked fibrosis of the wall²¹. This gives an impression of chronic cholecystitis on clinical and imaging ground. Furthermore, many gallbladder adenocarcinomas reveal only diffuse thickening of wall without any apparent mass lesion. When diffuse growth pattern is there, the gross distinction from chronic cholecystitis may be difficult and a significant minority of gallbladder cancers (up to 30%) are not apparent even at gross examination of specimen²³. This clearly necessitates the need for microscopic examination of each and every excised gallbladder specimen.

Limitations of the study:

Biochemical examination of the stones was not done at our institute. In tumour pathological staging we could not assess the lymphnode status and distant metastasis; and hence only pT status could be given.

Conclusion:

Histopathological evaluation of cholecystectomy specimens reveals a varied histopathological spectrum of underlying pathologies, with chronic cholecystitis being the most common lesion.

Gallstones are found in a majority of cholecystectomy specimens, irrespective of the nature of the lesions; which clearly highlights the role of gallstones as a prime risk factor for both inflammatory as well as neoplastic gallbladder diseases. Gallbladder carcinomas may frequently mimic chronic cholecystitis based on clinical and imaging parameters. Furthermore, an apparent mass lesion is not observed in many gallbladder specimens with malignant or premalignant lesions. Hence, such gallbladder malignancies may be easily overlooked on macroscopic examination of the excised specimen. As most of the malignant lesions in our study were reported as an incidental finding, we advocate routine histopathological examination of each cholecystectomy specimen.

Conflict of Interest: The authors declare that, there is no conflict of interest regarding the publication of this article.

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