A Prospective Study on Analysis of Histopathological Variations in Post Cholecystectomy Specimens Done for Benign Conditions in a Tertiary Care Hospital, Tirupati

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ABSTRACT

BACKGROUND

Cholecystectomy is a common surgical procedure done worldwide for both benign and neoplastic conditions. Cholecystectomy for benign conditions is performed based on clinical signs, symptoms, Ultrasound, CT. Hence there is fair chance of missing early malignant lesions like carcinoma-in-situ and other early carcinomas. Aim: The aim of the study is to analyse histopathological variations in post cholecystectomy specimens done for benign lesions.

METHODS

The study was conducted in Department of General Surgery, SVRRGGH, Tirupati, for a period of one year, from March 2019 to April 2020. This is a prospective Study conducted among 100 Patients, conducted over a period of one year from time of IEC approval from March 2019 to April 2020. All patients who underwent cholecystectomy for benign biliary disease and gall stone were included in the study. All patients with pre-diagnosed empyema gallbladder, gallbladder malignancy, gallbladder mass, and gallstones associated with obstructive jaundice are excluded from the study.

RESULTS

In our study, 100 cases of gall bladder disease were studied in the age group of 18 – 70 years, for a period of 1 year from March 2019 in the department of General surgery, SVRRGGH. Occurrence is high in patients of age group 18 – 45 years (65 %). The male to female ratio is 0.5:1 with female preponderance. The most common histopathologic finding was chronic calculus cholecystitis (59 %).Adenocarcinoma of gall bladder (2 %) of the cases with no preoperative suspicion of malignancy.

CONCLUSIONS

The occurrence of Incidental GBC found in my study is 2 %. Due to high estimate of residual disease, re-resection is still a curative option and is to be considered for pT2 & pT3, but not CBD removal. Prognosis usually is dismal, and five-year survival rates have been reported to be less than 5 % for more advanced stages.

KEYWORDS

Histopathology, Variations, Cholecystectomy, Specimen, Benign

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BACKGROUND

Cholecystectomy is a commonly performed surgical procedure worldwide for both benign and neoplastic conditions. Cholecystectomy for benign conditions is performed based on the clinical signs and symptoms, Ultrasound, and computed tomography scan. Early malignant lesions such as carcinoma-in-situ and other early carcinomas can be missed as routine histopathology of the specimen has not been followed up. This is deemed a selective approach that can exclude a valuable diagnosis of malignancies and other discrete precancerous pathologies such as porcelain gallbladder/polyps/cholesterosis.

In India, the prevalence of gallbladder stones has been documented adequately. In India itself, North India has a higher prevalence of gallstone disease than the South Indian population. The prevalence is higher in multiparous women. Though the prevalence of gallbladder stones has not been related to the prevalence rates of gallbladder stones and laparoscopic cholecystectomy, the prevalence for gallbladder carcinoma does depict an association. The pathogenesis of transformation of gallbladder stones to cancer is not clearly understood. The concentration of glucoursodeoxycholate, duration of the stones is said to contribute to the transformation to carcinoma.

Objectives

1. To study Ultrasound finding in patients with suggestive gall bladder disease.
2. To study the histopathological changes in the same patients.
3. To study relation between Ultrasound and histopathological finding.

METHODS

The study was conducted in Department of General Surgery, SVRRGGH, Tirupati, for a period of one year, from March 2019 to April 2020. This is a prospective Study conducted among 100 Patients, conducted over a period of one year from time of IEC approval from March 2019 to April 2020. All patients who underwent cholecystectomy for benign biliary disease and gall stone were included in the study. All patients with pre-diagnosed empyema gallbladder, gallbladder malignancy, gallbladder mass, and gallstones associated with obstructive jaundice are excluded from the study. Detailed history, clinical examination, and necessary investigations, including complete blood picture, liver function tests, and ultrasound abdomen, will be done for the patient presenting with right hypochondrial pain, jaundice, dyspepsia. Patients diagnosed as having gall stones and other benign biliary disease and will require simple cholecystectomy are taken into the study. The surgically excised gallbladder specimens will be sent for histopathological study. Patients with the positive histological correlation of carcinoma will be called up, further investigated, and treated depending upon the stage of the disease. There after they will be followed up for one year.

Statistical Analysis

The data was analyzed by IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, N.Y., USA) and GraphPad Prism version 9. Data is expressed using descriptive statistics such as Mean+/- Standard deviation or median with range. A chi-square test for association was conducted between gender and the presence of gall bladder disease.

RESULTS

In this study, 100 patients with symptoms suggestive of gall bladder disease were investigated preoperatively with Ultrasound and undergone, whether open or laparoscopic cholecystectomy. The post-surgical sample was sent for histopathological examination for the report, and it is correlated with USG findings. Most of the patients in this cohort were female (n= 66/100, 66 %), and males were 34 % (n = 34/100). Gall bladder disease more common in females. The mean and standard deviation of the age of patients in this cohort was 43.15±11.63. The minimum age of the patient was 22 years, and the maximum age was 70 years. The median age was 40 years, and the range of the patients was 49 years.

The sex distribution was analyzed between patients with age less than 45 years were compared to that those patients who had age above 45 years. A chi-square test for association was conducted between gender and the presence of gall bladder disease. All expected cell frequencies were greater than five. There was no statistically significant association between gender and the presence of gall bladder disease $\chi2(1) = 1.647$, $p = .199$. Females were in a higher proportion in both age groups.

	USG findings	Frequency
Valid	Acute Cholecystitis	17
	Chronic Cholecystitis	20
	Cholelithiasis	62
	GB Polyp	1
	Total	100

Table 1. Ultrasound Abdomen Findings of Patients

Ultrasound Findings of the Patients

Most of the patients were opined to have cholelithiasis on Ultrasound of the abdomen (62 %). The acute and chronic Cholecystitis was opined in the frequency of 17 and 20 percent, respectively.

Symptoms of the Patients

The main symptoms reported by the patients were pain abdomen and vomiting. Pain abdomen is seen in (97 %) of patients. Vomiting was seen in 51 % of patients. Tenderness was seen in 97 % of the patients. Three patients had only vomiting as presenting symptom with no pain abdomen requiring investigation for gall bladder disease. Vomiting was seen more commonly in acute and chronic Cholecystitis as compared to cholelithiasis and gall bladder polyp.

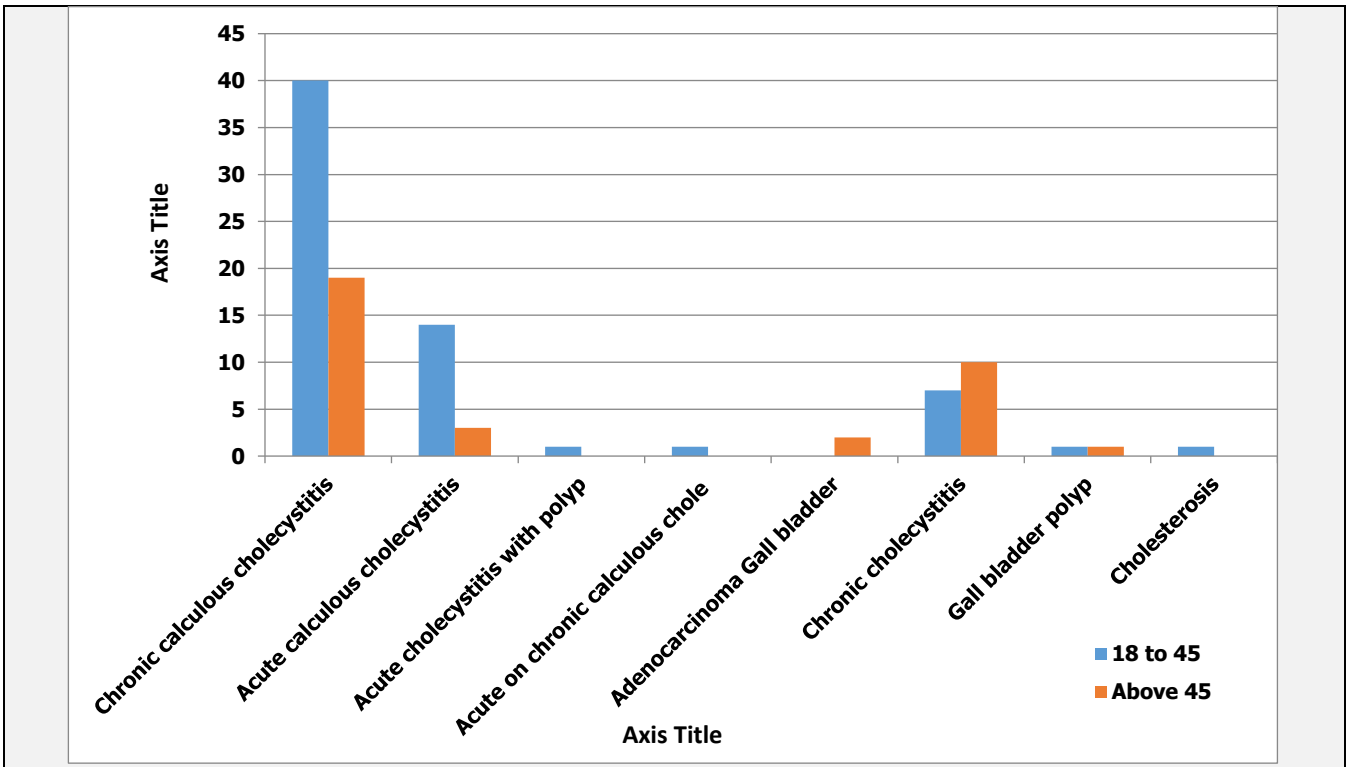

Figure 1. Bar Diagram Showing Relation of Sex with Histopathological Findings

Histopathology Finding	Frequency
Chronic calculous Cholecystitis	59
Acute calculous Cholecystitis	17
Acute Cholecystitis with polyp	1
Acute on chronic calculous Cholecystitis	1
Adenocarcinoma GB	2
Chronic Cholecystitis	17
Gall bladder polyp	2
Cholesterosis	1
Total	**100**

Table 2. Histopathological Findings

		Age Group		Total
		18 to 45	Above 45	
Histopathology finding	Chronic calculous cholecystitis	40	19	59
	Acute calculous cholecystitis	14	3	17
	Acute cholecystitis with polyp	1	0	1
	Acute on chronic calculous cholecystitis	1	0	1
	Adenocarcinoma GB	0	2	2
	Chronic cholecystitis	7	10	17
	Gall bladder polyp	1	1	2
	Cholesterosis	1	0	1
	Total	**65**	**35**	**100**

Table 3. The Relation between Age and Histopathological Findings

		Histopathology finding								
		Chronic Calculous Cholecystitis	Acute Calculous Cholecystitis	Acute Cholecystitis with Polyp	Acute on chronic Calculous Cholecystitis	Adenocarcinoma GB	Chronic Cholecystitis	Gall Bladder Polyp	Cholesterosis	Total
USG Finding	Acute cholecystitis	1	13	1	1	0	0	0	1	**17**
	Chronic cholecystitis	0	3	0	0	0	16	1	0	**20**
	Cholelithiasis	58	1	0	0	2	1	0	0	**62**
	GB Polyp	0	0	0	0	0	0	1	0	**1**
	Total	**59**	**17**	**1**	**1**	**2**	**17**	**2**	**1**	**100**

Table 4. Relation between Ultrasound Findings and Histopathology Findings

DISCUSSION

Carcinoma Gallbladder is the sixth most common malignancy of the gastrointestinal tract worldwide. Its the most common malignancy of the biliary tract. It is also associated with a pre-existing gall stone disease. Longstanding chronic inflammation by gall stones considered to have an important etiological role in carcinogenesis. The prevalence of gall stones in India is 2 to 29 %.[1] The occurrence of carcinoma gall bladder associated with gall stones varies from 0.3 to 12 %.[2,3] Cholecystectomy is the most commonly performed surgical procedure for gall bladder diseases. The majority of cholecystectomies are done for gall stones. Routine examination of gall bladder specimen shows a lot of interesting findings. All gallbladder containing stones should be removed surgically because of cancer risk, which is greater than the operative mortality risk.[4]

Cholecystectomy performed based on clinical, ultrasonological, and CT scanning misses a significant number of early malignant lesions of the gall bladder as early carcinoma remains undiagnosed without histopathology as it neither produces clinical symptoms or signs nor provides any clues on ultrasound assessment. To avoid blunders with bad consequences, therefore every cholecystectomy specimen should be routinely examined histopathologically.[5]

Calcification of gall bladder wall, presumably due to chronic inflammation (porcelain gall bladder is also associated with a small increase in the risk of gall bladder carcinoma. Cholesterosis of the gall bladder may be defined as a metabolic disease and not an inflammatory disease in which the mucosa of the gall bladder contains deposits of cholesterol and lipoid material. In advanced stages of the disease, cholesterol caliculi can be present in the lumen of the gall bladder. Cholesterosis is also a premalignant

condition that is associated with an increased risk of gall bladder carcinoma. Cholesterosis is associated with metaplasia, and it is often opined as cholelithiasis in the ultrasonogram. Associated carcinoma can be missed if the specimen is not subjected postoperatively for histopathological examination.

Carcinoma of the gall bladder is aggressive and presents as a late disease, and most of the patients are usually treated at advanced stages. The symptoms are usually indistinguishable from those of benign gall bladder disease, particularly in older patients. Jaundice and anorexia are usually late clinical presentations. .A palpable mass usually signifies a late sign/.

The prognosis is usually poor, and the five-year survival rates have been reported being less than 5 % in more advanced stages of carcinoma. Women in northern India (21.5 / 100,000) and Native American Indians (14.5 / 1000,000) have a high occurrence. Incidental carcinoma of the gall bladder is the gall bladder carcinoma that is to be suspected for the first time during cholecystectomy or to be found on the histopathological examination of the resected specimen. Its diagnosed incidentally be-cause of the inflammatory symptoms, which are related to the coexistent cholelithiasis or Cholecystitis. With the increasingly widespread acceptance of Laparoscopic Cholecystectomy and the difficulties in diagnosing Gall Bladder Carcinoma preoperatively, the number of cases of Incidental Gall Bladder Carcinoma during and after Laparoscopic Cholecystectomies has increased. Female sex and age are the demographic risk factors for GBC.

- The appropriate management and overall prognosis depend strongly on the staging of the tumor
- The AJCC TNM staging for GBC seventh edition (2010) is used.

Staging

Staging Primary Tumor

- Tx: Primary tumor cannot be assessed
- T0: No evidence of primary tumor
- Tis: Carcinoma in situ
- T1a: Tumor invades lamina propria
- T1b: Tumor invades muscle layer
- T2: Tumor invades perimuscular connective tissue, no extension beyond serosa or into Liver
- T3: Tumor perforates the serosa and/or invades structures such as the stomach, duodenum, colon, pancreas, omentum, or extrahepatic bile duct.
- T4: Tumor invades main portal vein or hepatic artery, or two or more extrahepatic organs or structures.

Staging Regional Lymph Nodes

- Nx: Regional lymph nodes cannot be assessed.
- N0: No LN metastasis
- N1: Metastasis to nodes along the cystic duct, CBD, hepatic artery, and or portal vein

Staging Distant Metastases

- M0 No distant metastases
- M1 Distant metastases.

Anatomic Stage / Prognostic Groups

- Stage 0 Tis No Mo
- Stage I T1 No Mo
- Stage II T2 No Mo
- Stage IIIa T3 No Mo
- Stage IIIb T1-3 N1 Mo
- Stage IVa T4 No-1 M1
- Stage IVb Any T Any N M1

Histologic Grade (G)

- Gx Grade cannot be assessed
- G1 Well-differentiated tumor
- G2 Moderately differentiated tumor
- G3 Poorly differentiated tumor
- G4 Undifferentiated tumor

Age Occurrence

In Srinivasan g et al. study, patients of age group 11-80 years were studied, and this study showed a peak occurrence in patients of age group 31-40 of 30.5 %.

Age-Wise	Siddiqui et al.[6]	Srinivasan G et al.[7]	Present Study
Most common age group	31 – 40years	31 – 40 years	18 – 45 years
Percentage	27.8 %	30.5 %	65 %

Table 5. Comparison of Age Distribution with Other Studies

Sex Occurrence

In Srinivasan g et al. study, the male to female ratio is 0.09:1. Female predominance is also reported in other studies.[8,9]

Surgical Procedure

In our present study, patients were subjected to laparoscopic cholecystectomy and open cholecystectomy, of which laparoscopic cholecystectomy was done for 87 %, and open cholecystectomy was done for 13 %.In Srinivasan et al. study, laparoscopic cholecystectomy was done for 83.3 %, and open cholecystectomy was done for 16.6 %.

Clinical Features

The presenting symptoms for a gall bladder pathology can vary from colicky abdominal pain, nausea/vomiting, fever, intolerance to fatty foods, and mass in the upper abdomen. The most common symptoms are abdominal pain, nausea/vomiting, and tenderness over the right hypochondrium.

In my study, abdominal pain was present in about 97 %, and vomiting was present in about 51 %. Tenderness over Right Hypochondrium was present in 96 % of the patient." In Siddiqui et al., abdominal pain was present in about 91.4 %, and vomiting was present in about 20 %. Tenderness over the right hypochondrium was present in 76 %. Gall bladder malignancy usually does not have any characteristic clinical features, with over 90 percent of patients presenting with symptoms of acute or chronic cholecystits"[10]

Symptoms	Siddiqui et al	Present Study
Pain	91.4 %	97 %
Vomiting	20 %	51 %
Tenderness	76 %	96 %

Table 6. Comparison of the Distribution of Symptoms with Other Studies

Histopathological Occurrence

Histopathological variations in post cholecystectomy were found to be chronic Cholecystitis, acute Cholecystitis, gall bladder polyp, and adenocarcinoma of the gall bladder. Of the above findings, the most common among all the three studies were found to be chronic Cholecystitis. In our study, the histopathological occurrence of chronic Cholecystitis was found to be 77 %. Acute Cholecystitis was found to be around 18 %. Occurrence of gall bladder polyp was found to be around 3 %occurrence of adenocarcinoma was 2 %. In Siddiqui et al. study, the occurrence of chronic Cholecystitis was found to be around 92 %. Occurrence of acute Cholecystitis was found to be around 4.5 %. Occurrence of gall bladder polyp was found to be 0.5 %. The occurrence of adenocarcinoma of the gall bladder was found to be around 2.7 %.

In Srinivasan et al. study, the occurrence of chronic Cholecystitis was found to be around 94.4 %. Occurrence of acute Cholecystitis was found to around 2.7 %. Occurrence of Xanthogranulomatouscholecystitis was found to be around 2.9 %. A similar study by Menon[11] also reports chronic Cholecystitis as a major histopathological finding in 64.8 % of cases. The common histopathological finding in our study was chronic Cholecystitis, and the specimens were reported as chronic inflammation with mucosa ulceration, denudation with infiltration of chronic inflammatory cells like neutrophils, macrophages, plasma cells with varying degree of fibrosis. Gall bladder polyp has an occurrence of 4 – 6 %. In our study, the occurrence of gall bladder polyp was seen in 3 cases. The lower number of occurrence can be attributed to the lower number of cases studied. The prevalence of gall bladder is higher in males than in females.

In our study, incidental carcinoma gall bladder was seen in 2 % of the cases. These gall bladders showed no gross abnormality preoperatively. In our study the low occurrence of malignancy is due to the high sensitivity to exclusion criteria, wherein preoperatively all patients with evidence of malignancy were excluded. All patients presented with longstanding symptoms of chronic Cholecystitis, There were no symptoms suggestive of underlying malignancy in our study. Over 90 percent of patients present only with symptoms of acute or chronic Cholecystitis. Even though Ultrasound has a high diagnostic accuracy, none of the two carcinomas in this series were picked on preoperative Ultrasound.

Therefore, the study advocates routine histopathology of all gallbladders removed at the surgery. The strong association between carcinoma gallbladder and gall stones necessitates the need for histopathology of specimen for all cases undergoing cholecystectomy for cholelithiasis. It is reported that longstanding mucosal irritation by stones can cause atypical cellular changes and increased cellular proliferation. In longstanding cases, the areas of hyperplasia can progress to metaplasia and carcinoma –in-situ.

Histopathology of adenocarcinoma was seen in 2 cases, of which both cases were well-differentiated adenocarcinoma. No case of squamous carcinoma was identified, or other variants of cancerous histology were seen. The two cases of incidentally diagnosed malignancies were associated with gallstones, which strongly supports the role of chronic irritation by longstanding gallstones as an etiological factor for carcinoma gall bladder. The patients were followed up for a period of 6 months to 1 year.

CONCLUSIONS

In my study, the occurrence of Incidental GBC is 2 %. Incidental GBC is becoming more common due to the widespread use of LC procedures for benign GB conditions. However, this is decreasing due to the use of ultrasound scanning. Open or Laparoscopic Cholecystectomy is the treatment forpTis& pT1. Due to the high estimate of residual disease, re-resection is still a curative option and is to be considered for pT2 & pT3, but not CBD removal. The type of hepatic resection does not affect disease outcome and is important to tumor-free margins. Prognosis is usually poor, and five-year survival rate is less than 5 % for more advanced stages.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
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