

## Histopathological findings of gall bladder specimen after cholecystectomy

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### Abstract

**Objective:** Cholecystitis is a generally widespread problem in adult population. Multiple findings have been found in gross and microscopic examination of gallbladder. Existence of stones is one of the known causative factors that lead to histopathological changes in gallbladder. It is also responsible for the development of gallbladder carcinoma. The purpose of this study was to find out the histopathology of gall bladder specimens following surgical intervention.

**Study design:** Observational study

**Place and duration of study:** This study was conducted at Surgery Department of Abbasi Shaheed Hospital and Pathology Department of Ziauddin Hospital, from January 2017 to February 2020.

**Material and Methods:** This observational study included 2,320 patients with acute or chronic cholecystitis secondary to gallstones that were admitted through the outpatient Department. Non-probability convenient sampling technique was used. Written and informed consent was taken from all the participants. Data was analyzed using SPSS version 20. Descriptive analysis was performed.

**Results:** A total of 2,320 gallbladder specimens that presented for histopathological examination during the study period were included into the study, with male to female ratio of 1:3. The highest prevalence was found in the age group of 31-50 years. The results of histopathological examination of these gallbladder specimens showed that chronic cholecystitis was found in 1353 (58.3%), acute cholecystitis in 469 (20.2%), Gangrenous cholelithiasis 33 (1.4%) and cholestrolosis in 333 (14.3%) patients. Dysplasia was found in 8 (0.34%) patients, and gall bladder carcinoma was detected in 16 (0.69%) patients. There were 2181 (94%) cases of calculi-cholecystitis. On morphological analysis, the commonest gall stones were made up of cholesterol and the most common lesion was chronic cholecystitis by histopathology.

**Conclusion:** This study concludes that the chronic calculi-cholecystitis was dominant in our population. It is assumed that routine histopathological examination following cholecystectomies essential for all gallbladder specimens even in the non-existence of macroscopic signs of carcinoma, which was the case in our patients.

**Keywords:** Gall bladder, histopathology, cholecystitis, cholecystectomy, Gangrenous cholecystitis, Dysplasia, cholestrolosis, gall bladder carcinoma

### Introduction:

Gallbladder is a small pear-shaped sac that stores and helps to concentrate bile. It is linked to the liver (which forms the bile) by hepatic duct. When food comprising fat enters into the small intestine, the hormone cholecystokinin is formed by discrete endocrine cells in intes-

tinal wall and is transferred to the gall bladder through the bloodstream. Due to this hormone, gall bladder contracts, forcing bile into common bile duct that aids in digestion of fat.<sup>1</sup>

Occasionally the substances contained in bile come together and crystallize in the gall bladder

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that produces gallstones. These tiny, solid concretions are more frequent in an individual over age of 40, especially in women and overweight people. They are responsible for irritation of the gall bladder's mucosal wall that can create hurdles to biliary tree and are responsible for swelling of gall bladder mucosa. A severe episode of pain also occurs through-out this period.

Gall stone disease has a high prevalence in the western world as well as in our country. 10% of adult patients have no symptoms of gall stones. The prevalence is affected with age, sex and ethnic group.<sup>2</sup> Gall stone disease (GSD) was formerly regarded as the disease of western population, due to changes in pattern of food utilization, but in the developing countries, it has now become an increasingly common cause of morbidity.<sup>3</sup> In the developed countries like UK, USA and Italy the rate of recurrence has been reported 10% to 20%.<sup>4</sup> Limited data from Pakistan has been found, but an earlier study in Southern Sindh area of Pakistan has reported a an incidence of gall stone disease in 9.03%.<sup>5</sup> Mostly an incidence rate of 4% in males and 14.2% in females is found in Pakistan.<sup>6</sup>

Gall stones differ in their composition, most of them are composed of cholesterol, the remaining being mixed and can be pigmented. Generally, cholesterol stones are the most common type. Stones that are having rich in bilirubin are known as pigment stones. Persistent gall stones also responsible to be a common risk factor in formation of carcinoma of gall bladder.<sup>7</sup>

It is confirmed that multiple risk factors are involved in GSD,<sup>8</sup> which includes ageing, gender, dietary habits, intake of high calorie, low fiber diet, refined carbohydrates in high amount, lack of physical activity, pregnancy, parity, heavy-weight and obesity.<sup>9</sup> Furthermore, the risk of disease increases with the increasing age in both male and female with a high rate of incidence from the range of 40 to 50 years of age.<sup>10</sup> It is stated that the ratio of females is three times more than males for this disease.<sup>11</sup> A mnemonic for remembering the risk factors linked with gallstones is female, fat, fertile and forty. Further-

more, females having a more risk to develop gall stones if they have used oral contraceptives pills, gave birth to 3 or more children or undergone for full-term pregnancies.<sup>12</sup> Symptoms of cholelithiasis are presented in the form of pain in the upper abdomen, indigestion to fatty food, nausea or vomiting, mass felt in right hypochondrium. Female gender with increasing age is an important risk factor for the gall stone formation. Risk factors that can be changeable are obesity, inactive life style result in hypomotility of gall bladder. Over weight patients have increased chances of cholecystitis.

Cholecystitis is one of the frequent problems that lead the patients to surgical intervention and in an emergency. Inflammation of gall bladder can be acute, chronic or acute on chronic cholecystitis. Presence of gall stones is the leading cause of cholecystitis in most of the cases.<sup>13</sup>

Gall bladder containing stones must be surgically removed because if they persist having a potential risk of formation of malignant disease. Pathological changes can differ from inflammation to malignancy.<sup>14</sup> Analysis of histopathology of gall bladder specimen is therefore compulsory for diagnosis of early carcinomas. Early diagnosis gives a good prospect of outcomes in patients with gallbladder carcinoma especially that discovered in stage-I disease.

A diverse histopathologic change that occurs in gall stone disease is gall bladder mucosal changes like acute inflammation, chronic inflammation, granulomatous inflammation, cholestrololysis, dysplasia and carcinoma. The mucus of gall bladder plays a regulatory role in gall stone formation as it regulates and supports the nucleation of stones. Mucus, calcium and lipids are combined to form the gallstones.<sup>15</sup>

The study focuses to enumerate the various consequences of routine examination of gall bladder specimen following cholecystectomy. A variety of patterns of histopathologic changes can be evaluated and most probable risk factors can be investigated in order to reduce the chances of disease.

Table 1: General description of patients with cholelithiasis. (n=2320)

Variable		Mean±SD n (%)
Age (years)		32.3 ± 5.3
Age (Categories)	< 20 years	55(2.37%)
	20 - 29	283(12.19%)
	30 - 39	505(2.76%)
	40 - 49	557(24.0%)
	50 - 59	503(21.68%)
	60 - 69	290(12.5%)
	70 - 79	104(4.48%)
	80 - >80	23(0.99%)
Gender	Male	588(25.3%)
	Female	1732(74.6%)

Table 2: General description of patients with cholelithiasis. (n=2320)

Variable		n (%)
Types	Acalculous cholecystitis	139 (6%)
	Calculous cholecystitis	2182 (94%)
Surgery	Laparoscopic cholecystectomy	2042 (88.0%)
	Open cholecystectomy	278 (11.98%)

Table 3: Distribution of cases according to histological examination of the gall bladder specimens

Variable	Number of patients (n=2320)	Frequency (%)
Acute cholecystitis	469	20.2%
Chronic cholecystitis	1,353	58.3%
Cholesterosis	333	14.3%
Xanthogranulomatous cholecystitis	25	1%
Follicular cholecystitis	21	0.9%
Hyalinizing cholecystitis	6	0.25%
Gangrenous cholelithiasis	33	1.4%
Malignant in elective cholecystectomy cases, operated for cholelithiasis	16	0.69%
Atypia	15	0.64%
Dysplasia	8	0.34%
Focal intestinal metaplasia	25	1%
Porceline gall bladder	3	0.13%
Adenomyomatosis	13	0.56%

**Material and Methods:**

The observational study consisted of 2,320

patients with acute or chronic cholecystitis secondary to gallstones admitted through the outpatient department. Non-probability convenient sampling technique was used. Written and informed consent was taken from all the participants. This study was carried out over a period of about three years from January 2017 to February 2020.

Patients with confirmed cases of carcinoma gallbladder, on clinical findings and that were confirmed by ultrasonography or CT scan, were excluded from the study. Gallbladders showing gross abnormalities that were indicative to localized or infiltrative malignancy during surgery were also excluded. The inclusion criteria was, all the cases of elective or emergency cholecystectomy, done for chronic or acute cholecystitis, including all age groups. Pre-operative assessment was done with a complete detailed history and thorough clinical examination of the patients. The systemic analysis was done in order to assess any co-morbidity. Baseline and particular investigation especially ultra-sonography of the abdomen was done in all patients.

Laparoscopic cholecystectomy was carried out in all cases but had to be changed into open procedure in the minority of cases where anatomical alteration and dense adhesions hindered any further procedure of laparoscopic cholecystectomy. All gallbladder specimens, also including those with no noticeable gross anomaly, were sent for histopathology. Data was analyzed using SPSS version 20.0. Descriptive analysis was performed.

**Results:**

Over a period of three years, 2,320 patients with symptomatic gallstones were admitted for cholecystectomy. There were 1732(74.6%) females and 588 (25.3%) males with a male to female ratio of 1:3. The age ranged from 19 to 80 years with the mean age of 32.3 ± 5.3 years (Table 1). Majority of patients presented with upper abdominal pain of varying duration. Majority of cases were found to be associated with stones 2182 (94%). Only few cases were, without gallstones 139 (6%) (Table II).

In Table III, 2320 specimens of gall bladder showed evidence of chronic cholecystitis,<sup>1</sup> 353(58.3%) cases, 469(20.2%) acute cholecystitis with mucocele, 333(14.3%) cholesterolosis with empyema, Gangrenous cholelithiasis 33(1.4%), Xanthogranulomatous cholecystitis 25(1%), Focal intestinal metaplasia 25(1%), Malignancy was found in cholecystectomy specimen 16(0.69%), Follicular cholecystitis 21(0.9%).<sup>13</sup> gallbladders (0.56%) showed evidence of adenomyomatosis.<sup>15</sup> gall bladder showed evidence of atypia(0.64%).

Table I shows that majority of patients were of 3rd, 4th and 5th decade of life having 505(2.76%), 557(24%) and 503(21.68%) respectively. The age range was from >20 - <80 years.

Table II shows laparoscopic cholecystectomy was performed in all cases 2042 (88%) but had to be converted to open procedure in few cases 278 (11.98%) where anatomical alterations and dense adhesions stopped any further progress in laparoscopic cholecystectomy.

#### Discussion:

It was also obvious that the frequency of gall bladder disease was more in females in comparison with males, particularly during the premenopausal phase. This finding is consistent with the previous Pakistani Hafiz et al.<sup>16</sup> study and other international studies conducted in past.<sup>17</sup> These findings were correlated with our studies also. The difference is due to the increased levels of estrogen which is known as the primary sex hormone in the female gender. The elevated levels of estrogen augment the excretion of cholesterol in bile which in turn increases its saturation resulting in the development of cholesterol gallstone.<sup>18</sup>

In our study, gall stone disease was predominantly found in females (74.6%) as compared to males (25.3%). Female sex hormones play an important role, in particular between the ages of 30 and 50 years. Zafar SN et al.<sup>19</sup> studied the morphologic features of the gall bladder in 415 specimens of gall bladder following cholecystec-

tomy. Females were more affected with male to female ratio of 1:5. It was also consistent with our study, in which, male to female ratio was 1:3. Most of the cases were seen in the 4<sup>th</sup> and 5<sup>th</sup> decade, similarly, in our studies most of the cases were found in 3<sup>rd</sup>, 4<sup>th</sup> and 5<sup>th</sup> decades. Associated chronic cholecystitis was seen in 85.3% of cases in the Zafar study.<sup>19</sup> These results have coincided with results of our study that proved 58.3% cases were associated with chronic cholecystitis.

25(1%) cases of xanthogranulomatous cholecystitis and 25(1%) cases of focal intestinal metaplasia included in our study were of age 30 and 40 years respectively. These results were different from a study done by Singh N et al in which he reported the cases of xanthogranulomatous cholecystitis in 6<sup>th</sup> and 7<sup>th</sup> decade of life.<sup>20</sup> Di Ciaula et al found that the commonest age group for cholelithiasis was below 30 years.<sup>21</sup> that was inconsistent with our study.

Persistent chronic inflammation, infection, and stones that retained for a longer period of time are presently believed to be the causes of malignant change in the epithelium of gallbladder.<sup>22</sup> Various studies have long been presenting the relationship between gallbladder cancer, and the chronic inflammation which is caused by gallstones.<sup>23</sup> Carcinoma of gallbladder was detected in 16 (0.69%) of cholelithiasis cases. Prolonged chronic inflammation that is caused by gallstones are responsible for this association.<sup>24</sup> on the other hand, only inflammation at the gallbladder wall is generally not a definite sign as it can also be found in chronic inflammatory diseases.<sup>25</sup>

Our results showed that the frequency of chronic cholecystitis was 1353(58.3%), and was the most common pathology among the diseases associated with unpredicted gallbladder cancer and our results are consistent with this fact.<sup>26</sup> Deng et al.<sup>27</sup> also found a connection between cancer and acute cholecystitis. This did not coincide with our study in which pathological examination discovered malignancy in 16 patients who had an initial diagnosis of chronic cholecystitis. There are two important carcinogenesis

models. These are Metaplasia-dysplasia-carcinoma and adenocarcinoma. Numerous studies have shown relations between pyloric metaplasia and dysplasia, pyloric metaplasia and cancer, and also intestinal metaplasia and pyloric metaplasia, dysplasia, and cancer.<sup>28</sup> In this study, the dysplasia-cancer association was detected in only 8 (0.34%) cases.

The most frequent histo-pathological finding in our study was chronic cholecystitis; 1353 (58.3%) specimens were reported as chronic inflammation with ulceration of mucosa, denudation, metaplasia to dysplasia and infiltration of wall of gallbladder by chronic inflammatory cells like neutrophils, macrophages, plasma cells and varying degrees of fibrosis. A similar study by Memon<sup>29</sup> also reports chronic cholecystitis as major histo-pathological finding, identified in 64.8% of cases. These results were also consistent with our studies.

Empyema of the gallbladder is frequent complication<sup>30</sup> In this study, 469 (20.2%) cases were detected as acute cholecystitis with empyema of gallbladder. This is in contrast to 31.5% of cases of empyema associated with cholecystitis as suggested by Memon.<sup>29</sup>

In our studies, incidental carcinoma of the gallbladder was found in 16 cases. The incidence of gallbladder malignancy in this study was significantly low as compared to other studies, which shows chances varying from 6.9 to 12 percent.<sup>31</sup> The low prevalence of carcinoma cases in our study can be attributed to high sensitivity to exclusion criteria, where all patients with any indication of malignancy before the operation were excluded from the study. In addition, low incidence of malignancy in our patients can also be due to increased recognition and early decision taking for laparoscopic cholecystectomy. Samad<sup>32</sup> suggests an incidence of 1.1% of malignancy in patients following cholecystectomy for recognized chronic cholecystitis with cholelithiasis.

Even though, there are numerous pre-malignant conditions exist but carcinoma gallbladder has a

strong correlation with gallstones.<sup>33</sup> The strong connection between the carcinoma and gallstones paid attention to histopathology of specimen in all cases of cholecystectomy for cholelithiasis, regardless of presence or absence of any gross abnormalities. We therefore recommend to send every specimen for histopathology, to detect carcinoma in early stage, which is usually curable.

#### **Conclusion:**

This study concluded that the most generally involved age group for cholelithiasis was found between 30-50 years. Female were more frequently affected as compared to males. Cholelithiasis was found as the most common causative factor, for causing carcinoma gallbladder, thus, histopathology of the gallbladder specimens after cholecystectomy is very important, to detect and treat the gallbladder carcinoma early.

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#### **Role and contribution of authors:**

Dr. Bushra Tasneem, collected the data, made result and wrote the article.

Dr. Aisha Tasneem, helped in collection of data

Dr Fauzia Lateef, collection the data, references and reviewed all slides of resected specimen for all histopathology and helped in writing the article.

Dr Saba Jamal, collected the data and helped in introduction writing.

Dr Rahil M Rehman, critical review the article and made final changes.

Dr Abdullah Muttaqi, went through the article and advised useful changes.

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