

Original Research Article

Gall bladder stones and the associated histopathology— a tertiary care centre study

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ABSTRACT

Background: Gall stones form one of the main reasons for recurrent upper abdomen pain. Cholecystectomy has turned out to be one of the commonest laparoscopic procedures done all over the world. The objectives of the study were to analyse the histopathological changes in gallstone disease and to study the clinical and biochemical factors that are seen in gall stone disease.

Methods: This was a hospital based cross sectional study conducted at a tertiary care centre from January 2013 to December 2014. 108 patients admitted with diagnosis of cholelithiasis and posted for cholecystectomy were studied. Their clinical and biochemical data and post-operative stone analysis results and histopathological reports were collected and analyzed.

Results: 63% of the patients were females with a female to male ratio of 1.7:1. Of the group, 64.8% had a BMI between 25 and 29.9. 65.7% patients got operated within one year of the onset of symptoms. Serum cholesterol levels were found elevated in majority of patients. 61% patients had multiple gall stones. 62% had stones composed of cholesterol, bilirubin, calcium carbonate and calcium oxalate. 102 out of the 108 specimens showed histological features of chronic cholecystitis only. One case showed a premalignant change in the form of pyloric metaplasia.

Conclusions: Cholelithiasis is seen mostly in females, most of them having elevated cholesterol levels. The commonest histopathological change associated with cholelithiasis is chronic cholecystitis. Premalignant lesions are seen only in a small minority only. Hence early elective cholecystectomy can prevent malignant transformation in asymptomatic gall stones.

Keywords: Biliary pain, Cholecystitis, Cholelithiasis, Gall bladder, Gall stone

INTRODUCTION

Biliary lithiasis has been a common disease all over the world. Gallstones are among the most common gastrointestinal conditions presenting with acute abdomen pain and requiring hospitalization in otherwise healthy people. More than half of the cases are asymptomatic, usually detected during an abdominal ultrasound.¹ Although most patients remain

asymptomatic from their gallstones, some patients develop symptoms, the 'biliary colic' being caused by a stone obstructing the cystic duct.

Coexistence of gallstones with cholecystitis, hyperplasia, intestinal metaplasia, and even carcinoma has been reported. Cancer of the gallbladder is found two to three times more commonly in women than men, supposedly because of the higher incidence of gallstones in women. Among the factors associated with an increased risk for

developing gallbladder cancer, gallstones are the most common because of the high prevalence in the general population and also because of their relationship with chronic inflammation. The incidence of gallbladder cancer is found to be seven times more in the presence of cholelithiasis and chronic cholecystitis. In addition, the risk for developing gallbladder cancer is also higher in patients with symptomatic gallstones. These facts prompted William Mayo to put forth his famous aphorism: 'There is no innocent gallstone'.

Most of the studies done to identify the risk factors for biliary stones have zoomed in on the hyper saturation of cholesterol in bile in the nucleation process.² However, gall bladder stone composition is supposedly heterogeneous, and has been found to differ within and without populations.^{3,4}

The treatment options for gallstone disease varies from bile salts dissolution, laser fragmentation, extracorporeal shock wave lithotripsy, endoscopic extraction and classical surgery. Bile acid therapy is only effective in some cholesterol gallstones and ineffective in treating calcium bilirubinate or calcium carbonate/phosphate stones. It is therefore ideal that the composition of the stones be determined to select the treatment of choice.

As per literature, it is evident that gallstone disease has a multifactorial causation, including previous gall bladder infection, decreased gall bladder motility after bariatric surgery and weight loss, ileal diseases like Crohn's, haemolytic diseases, familial hypercholesterolemia, as well as metabolic defects in hepatic bilirubin glucuronidation.⁵⁻⁹

The cumulative probability for developing biliary colic after 10 years is found to range from 15 to 25%. The operative mortality of elective cholecystectomy is usually less than 0.5%. However, increased mortality is seen in elderly persons (>60 year of age), and also in those with complications such as acute cholecystitis.

A better understanding of the risk factors for gall bladder cancer and the premalignant lesions of the gall bladder could help in proper selection of prophylactic cholecystectomies and thus reduction in morbidity as well as mortality. With this background, we studied the commonest reason for cholecystectomy, that is cholelithiasis. This study is carried out to study diverse histopathological changes in the gallbladder as a result of cholelithiasis and the clinical biochemical and the stone related factors affecting them.

The primary objective of the current study was to analyse the various histopathological changes occurring inside the gallbladder in gallstone disease. The secondary objectives were to study the premalignant and malignant changes in gallbladder in gallstone disease as well as to analyse the various clinical, biochemical and stone related factors that affect the histological changes.

METHODS

The study was designed as a hospital based Cross-sectional study. The study setting was the General Surgery department of Government Medical College Trivandrum, Kerala, India. This is one of the oldest medical colleges in the country and caters to the health care needs of a large number of patients from the southern districts of Kerala, India. The study period was for 2 years, from January 2013 to December 2014. The study subjects included all patients with documented gall stones and underwent elective cholecystectomy at our institution during the study period.

Inclusion criteria

Patients with diagnosed gall stones and aged between 12 to 80 years.

Exclusion criteria

Patients with documented gall bladder pathologies other than stones. Non-random sampling method was used. All consecutive patients fulfilling the eligibility criteria were enrolled in the study. Sample size was estimated based on a similar study (Khanna R et al) which studied the histopathological changes in the gall bladders of Indian patients with gall stones.¹⁰ As per this study, gross mucosal changes were noted in 64.5% and in microscopic epithelial changes were noted in 69%.

Formula used for sample size estimation was: $n = (Z\alpha)^2 pq/d^2$, where n =sample size, $Z\alpha=1.96$, p =prevalence, $q=100-p$, $d=20\%$ of prevalence. Substituting the values into the formula, n was found to be 54. It was decided to enrol double the number of calculated sample size to account for the design effect, as the sampling technique was not simple random. Hence the final sample size was set at 108. Before starting the study, the Institutional Research Committee clearance was obtained. Also approval from the Human Ethics Committee of the institution was obtained. The patients were informed about the study and written consent was recorded from all willing participants. Patients admitted with diagnosis of cholelithiasis for surgery were interviewed with the performa and details were collected.

During history taking, the variables recorded included demographic details, anthropometric data, family history of gall stones, drug history and details of symptoms. Blood parameters including haemogram, liver function test, serum cholesterol were also recorded. The patients underwent evaluation and treatment as per the departmental protocols. The patients were posted for open or laparoscopic cholecystectomy as per individual preferences and based on case characteristics. Intra-operative findings were noted in detail. Postoperatively the stone was collected and stone analysis was done. The stone was analysed for the contents and number. The removed gall bladders were subjected to detailed

histopathological examination. The histopathological results of cholecystectomy specimen were analysed in detail to record the changes in the tissues.

All collected data were entered into a structured performa. For statistical analysis, 'Epi Info'(CDC) was the software used. Univariate analysis was mostly required. Quantitative data was described as mean and standard deviation and categorical data using percentages. The level of statistical significance was set at a p value less than 0.05 wherever relevant.

RESULTS

The study was conducted on 108 patients with gall stones who underwent cholecystectomy for gall stones. The study was aimed at finding the various histopathological changes seen in gall bladder associated with gall stones and the various factors affecting them. At the end of the study, 108 patients who underwent cholecystectomy for cholelithiasis were studied. Of the 108 patients included in this study 78 patients (72%) were between the age group 31 to 60 years. No age group was exempted.

Most of the patients (63%) were females with a female to male ratio of 1.7:1. 64.8 % of patients had a body mass index (BMI) between 25 to 29.9. 71 patients (65.7 %) got operated within one year of onset of symptoms of colicky pain. 14 (12%) patients had symptoms for duration between 1 and 2 years and 15 patients (13.8%) patients had symptoms for duration between 2 and 5 years. Of the 68 female patients studied 41(60.2%) females had 2 children. 11 patients had history of bone and joint pathologies. None had history of total parenteral nutrition (TPN), estrogen administration or typhoid fever.

The mean haemoglobin of the study group was 12.63 grams per decilitre (gm/dl) with 95% confidence interval between 12.31 and 12.95gm/dl. The mean value of total leukocyte count of the study group was 8055 with 95% confidence interval between 7561 and 8549. The mean erythrocyte sedimentation rate (ESR) was 27 millimetre in first hour (mm/hr). The mean platelet count was 2.76 lakh cells per cubic millimetre (mm³).

The mean value of total bilirubin was 1.017 milligrams per decilitre (mg/dL) with 95% confidence interval between 0.76 to 1.27mg/dL. The mean value of direct bilirubin was 0.33mg/dL with 95% confidence interval between 0.23 to 0.43mg/dL. The mean aspartate transaminase (AST/SGOT) was 40.81 international units per litre (IU/L) with 95% confidence interval between 35.88 to 45.75IU/L. The mean alanine transaminase (ALT/SGPT) was 50.57IU/L with 95% confidence interval between 41.44 to 59.71IU/L. Mean value of alkaline phosphatase was 80IU/L. Mean total protein value was 6.28 grams per decilitre (g/dL). Mean albumin value was 4.12g/dL. The mean serum cholesterol value was 221.92 milligrams per decilitre (mg/dL) with a 95% confidence interval between 214.35 and 229.48 (Table 1).

Table 1: Distribution of serum cholesterol.

Serum cholesterol value		
Mean		221.92
95% confidence interval for mean	Lower bound	214.35
	Upper bound	229.48
Std. deviation		39.671
Median		214.00
Minimum		132
Maximum		302

Among the 108 patients studied, 66 (61%) had multiple gall stones. 39 (36%) patients had single gall stones while only 3 patients had 2 gall stones inside. Of the 108 gall stones studied, 62% (67 patients) had stones composed of cholesterol, bilirubin, calcium carbonate and calcium oxalate. 30.5% (33 patients) had stones composed of cholesterol, calcium carbonate and calcium oxalate. 5 patients had stone composed of cholesterol, bilirubin and calcium carbonate (Figure 1).

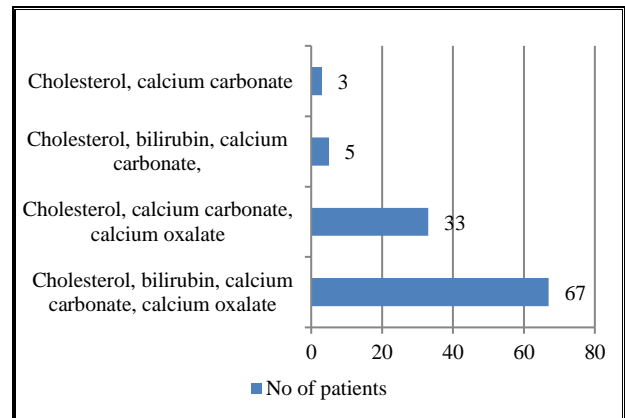


Figure 1: Distribution of chemical composition of gall stones.

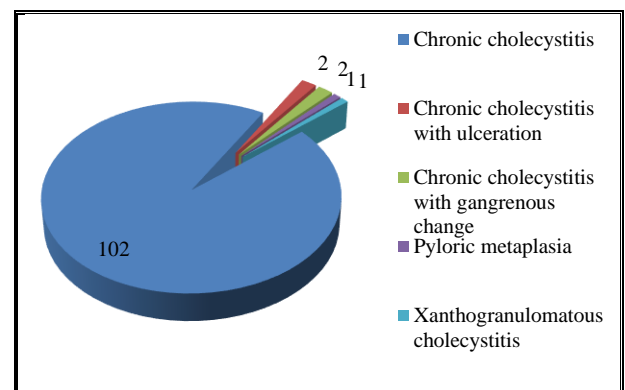


Figure 2: Distribution of histopathological changes in gall bladder.

Of the 108 gall bladder specimens studied, 102 specimens showed only features of chronic cholecystitis. Two specimens showed chronic cholecystitis with ulceration while two specimens showed chronic

cholecystitis with gangrenous change. Only one specimen (0.92%) showed premalignant lesion in the form of pyloric metaplasia. One specimen showed features suggestive of xanthogranulomatous cholecystitis. No specimen had underlying histopathological features of malignancy (Figure 2).

DISCUSSION

The main sufferers were females with a female to male ratio of 1.7:1, an incidence reported in literature and many other studies. In the study by Giri et al, the female:male ratio was 1.5:1.¹¹

Early onset of gall stone disease is noted in women in India. Gall stones are the commonest associated risk factor with carcinoma gall bladder, and are found to occur at a younger age in India, the correlation being approximately 60 to 90%. The duration of symptoms was less than 1 year in 65.7% of patients. This is considerably less compared to other studies. In a study by Tyagi et al the average duration of illness was 2.8 years.¹² The histopathological changes are supposed to depend on the duration of gall stones.^{13,14} Majority of the females: 41 out of 68: had 2 children.

Serum cholesterol levels were found elevated in majority of patients with a mean value of 221.92mg% while other blood parameters studied did not show any significant deviation from normal range. The high concentration of cholesterol in gallstones has been the basis for the accepted use of bile acids as a non-surgical treatment for gall bladder stones.

61% of the studied patients had multiple gall stones. In a study by Mathur et al, the number of stones varied from a single calculus in 39.6% cases, double in 8.8% and multiple in the remaining majority: 51.6%: cases.¹⁴ 62% of the patients had stones composed of cholesterol, bilirubin, calcium carbonate and calcium oxalate. Mixed stones formed the majority which is similar to most of the other studies. In the study by Tyagi et al, gall stones were of mixed variety in as high as 78.2% of the cases.¹² In the study by Mathur et al, mixed gall stones were found in 60.4%.¹⁴

102 out of the 108 specimens showed features of chronic cholecystitis only. Only one case showed premalignant change in the form of pyloric metaplasia. But in most of the other studies the premalignant and malignant changes are seen in higher numbers. Mathur et al reported cholesterosis in 6% cases, cholecystitis with hyperplasia (both adenomatous and adenomyomatous changes) in 8% cases and cholecystitis with metaplasia in 18% cases, while 2% cases had carcinoma.¹⁴ In the study by Giri et al, epithelial hyperplasia was observed in 46.20%, intestinal metaplasia in 25.54%, cholesterosis in 14 7.61% and dysplasia in 2.17% specimens.¹¹ In another study by Abassi et al, 2 patients out of 100 had carcinoma.¹⁵ In the study by Tyagi et al, chronic

cholecystitis was the main histological diagnosis (50.8%). Other lesions observed were adenomyomatosis (8.2%), adenomatous hyperplasia (10.1%), granulomatous cholecystitis (4.1%), cholesterosis (2.7%), acute cholecystitis (4.1%), acute-on-chronic infection (10.8%), sub-acute cholecystitis (2.4%) and carcinoma gall bladder (6.8%).¹²

The factors affecting the premalignant lesion could not be assessed as there was only one specimen which showed premalignant change and there were no malignant changes detected. The low incidence of premalignant and malignant change observed in this study may be because of the short duration of illness.

Present study had a few limitations in that people with asymptomatic gall stones were not separately studied and the relatively smaller sample size which could have skewed the proportions to some extent. Another shortcoming in our study was the absence of haemoglobin electrophoresis to rule out subclinical sickle cell trait. Nevertheless, we were able to elucidate enough information from present data

CONCLUSION

To summarize, majority of the patients with cholecystitis are females who get operated within 1 year of onset of symptoms, showing the accessibility of health care facilities and the health consciousness of people. Most of the patients have elevated serum cholesterol values which could indicate an underlying predisposing factor. Also a large majority of the patients have multiple gall stones, most of which are of mixed type, composed of cholesterol, bilirubin, calcium carbonate and calcium oxalate. The most common histopathological change that can be identified is chronic cholecystitis, while premalignant lesions like pyloric metaplasia are very rare. We conclude by stating that early cholecystectomy in symptomatic patients can be effective in aborting the onset of malignant transformation.

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