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Spectrum of Histopathological Changes in Cholecystectomy Specimens and its Correlation with Gallstones -A Prospective Study of 339 Cases

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Abstract: Gallbladder is affected by a wide spectrum of diseases ranging from non-neoplastic lesions like congenital anomalies, gallstones and its complications, non-inflammatory, inflammatory, to the neoplastic lesions .The aim of the study spectrum of histopathological changes in cholecystitis. The objectives were to study the histomorphology and frequency of various gall bladder diseases among specimens received and to correlate the various types of mucosal responses to different gallstone characteristic (like type, number, size volume and weight). Gall bladder specimen after cholecystectomy of patients who was admitted in ward surgery of BPS GMC, Khanpur Kalan, Sonepat.Place of study:-Department of Pathology, BPS GMC Khanpur Kalan, Sonipat. Study design- Prospective study. Out of 339 cases, two hundred and ninety seven (87.61%) patients studied were females, whereas 42 (12.39%) cases were males. Male to female ratio was 1:7.07. Out of the 339 cases, 234 (69.7%) had mixed stones, followed by pigment 44(13%) cases and cholesterol31 (9.1%) and 27 (8.1%) had no stones. 126 (37%) had single stone, nine had (3%) double and the remaining 195 (58%) had multiple stones. Conclusion: The histopathological spectrum of gallbladder lesions includes chronic cholecystitis and associated mucosal alterations and lesions like metaplasia, dysplasia and carcinoma. Variants of chronic cholecystitis such as xanthogranulomatous, granulomatous and follicular cholecystitis were also noted. To conclude, it was seen that the average weight, volume and size of the gall bladder significantly correlated in increasing order with cholecystitis, hyperplasia, metaplasia and carcinoma.

Keywords: cholecystitis, hyperplasia, metaplasia, carcinoma

INTRODUCTION

The gall bladder is the most commonly surgically resected organs and presents with a varied spectrum of diseases.

The diseases range from congenital anomalies, cholelithiasis, inflammatory and non inflammatory diseases to non invasive and invasive neoplastic diseases.

Cholelithiasis has been described as a disease of civilization.it constitutes a significant health problem in developed societies, affecting 10-15% of the adult population [1-3]. Whereas it is less prevalent in the developing populations that still consume traditional diets [4]

MATERIAL AND METHODS

The present study was conducted on 339 cholecystectomy specimens after due approval of project by the post graduate board of studies that includes ethical considerations. The stones were assessed for various parameters i.e. Number, size, weight, volume and morphological type.

- **Source of sample:** Gall bladder specimen after cholecystectomy of patients who was admitted in ward surgery of BPS GMC, Khanpur Kalan, Sonepat.

- **Place of study:** Department of Pathology, BPS GMC Khanpur Kalan, Sonipat.
- **Study design:** Prospective study

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The following methods were used to assess gallstones:-

Physical characteristics

- Number: single / double / multiple.
- Size: average of two major diameters with a vernier calliper (accuracy: 0.01 cm) was determined for size. In the event of multiple gallstones, the diameter of largest and smallest stone was recorded.
- Weight: weight determined using electronic analytical and precision balance (accuracy: 0.001 gm).
- Volume: volume was determined according to water displacement (accuracy: 0.1 ml).

Morphological characteristics

- Cholesterol: solitary, oval, large, yellow white. Cut section- radiating glistening crystals.
- Pigment: multiple, small, jet black, mulberry shaped. Cut section- soft and black.
- Mixed: multiple, multifaceted, variable size. Cut section- laminated alternating dark pigment layer and pale white layer.

The following methods were used to assess gallbladder

- Wall thickness: average wall thickness was calculated by measuring the maximum and minimum gallbladder wall thickness. A gall bladder wall ≥3 mm in thickness was defined as thickened.
- Size of gall bladder: normal size range was taken as 4-6.5 cm along the longest axis.

The following **microscopic diagnostic criteria** will be used

- Cholecystitis: included chronic cholecystitis, acute on chronic cholecystitis, chronic active, follicular and xanthogranulomatous cholecystitis, cholesterolosis, mucocoele.
- Hyperplasia: included both adenomatous and adenomyomatous hyperplasia.
- Metaplasia: included both intestinal and pyloric metaplasia.
- Carcinoma: included both carcinoma in situ and invasive carcinoma.

The various morphological responses were then categorized under four broad categories – cholecystitis, hyperplasia, metaplasia and carcinoma. Statistical analysis was performed by using analysis of variance (anova) for averages and chi-square test for contingency tables and proportions.

RESULTS

Out of 339 cases, two hundred and ninety seven (87.61%) patients studied were females, whereas 42 (12.39%) cases were males. Male to female ratio was 1:7.07.

We have taken seven cm as average length of gall bladder. Cases having length less than seven cm are considered as fibrotic which constituted 123(36.28%) of total sample, those with length of seven cm were 59(17.4%) and above the length of seven cm were157 (46.31%) as enlarged. Average gall bladder wall was found to be normal (<3 mm) in 219 cases, while it was thickened (≥3 mm) in the remaining 119 cases.

Out of the 339 cases, 234 (69.7%) had mixed stones, followed by pigment 44(13%) cases and cholesterol 31(9.1%) and 27 (8.1%) had no stones. Hence, the most common type of stone encountered was mixed type and the least common was cholesterol type.

Of the 339 cholecystectomy specimens 126 (37%) had single stone, nine had (3%) double and the remaining 195 (58%) had multiple stones. Almost all the cholesterol stones were single in 30(96.8%) cases, one case which had two cholesterol stones (3.2%). Pigment stones were single in 22(50%) cases and multiple in 20(45.5%) cases and two stones in one case (2.3%).

Of the 237 mixed stones only 47 (19.8%) were single, seven (3%) double and remaining 175 (73.8%) were multiple. No case of multiple cholesterol stone was noted. It is evident in our study that cholesterol stones occurred predominantly singly and mixed stones in multiple numbers.

Size of the stones showed correlation with the type of stone. The largest stone was of mixed type which were 8x8 cm , multiple in number and smallest size was pigment stone 0.2x0.2cm.

Weight of stone with type of stone mixed stones weighed the most with an average of 4.5 gm per stone with maximum weight being 30 gm and minimum 0.0002 gm. Minimum average weight (0.002gm) was found to be of mixed stone, the average weight of pigment stone was 1.6gms. While that of cholesterol stone was 1.48gm.

Association between volume and type of stone

Mixed stones had the maximum average volume of 3.9 ml. In discordance to weight, pigment stones had the minimum average volume of 1.2ml, cholesterol stone had an average volume of 1.6ml. Mixed stones had maximum volume being 28.4ml and minimum being 0.2 ml of pigment stone

DISCUSSION

Age wise distribution of 339 cases of cholecystectomy

Mathur *et al*., [5] found out that eighty (24.24%) patients belonged to the age group of 40-49 years whereas study by mittal *et al*., [6] in their study found that the mean age of diagnosis was 56.2 years (range 44-72 years). Sood *et al*., found that the mean age in there study was 43.56 years.

Association with type of stone and number of stones

Our study with sample size of 339 cholecystectomy specimens 126 (37%) had single stone, nine (3%) had double and the remaining 195 (58%) had multiple stones.

Association between size, weight, volume and type of stone

In this study the size of the stones showed correlation with the type of stone. The largest stone was of mixed stone which were 8x8 cm multiple in number and smallest size was of pigment stone 0.2x0.2cm.

Our study shows that mixed stones weighed the most with an average of 4.5 gm per stone with maximum weight being 30 gm and minimum 0.0002 gm. Minimum average weight (0.002gm) was found to be of mixed stone, the average weight of pigment stone was 1.6gms. While that of cholesterol stone was 1.48gm.

In the present study mixed stones had the maximum average volume of 3.9 ml with maximum volume of a mixed stone being 28.4ml and minimum value being 0.2 ml. In discordance to weight pigment stones had the minimum average volume of 1.2ml.

In study by Mathur *et al.*, [5] some other parameters such as weight, volume and size of stone were correlated with the type of stone. It was found that mixed stones had the maximum average weight (4.574 gm) and volume (4.793 ml), while they were minimum in cholesterol stones (0.809 gm and 0.736 ml respectively),which is on concurrence with our study the where maximum volume and weight was of mixed stone .the minimum weight and volume were of pigment stone sin our study.

The findings were almost opposite in case of size of stones, where cholesterol stones (1.348 cm) had the maximum average size and mixed stones (1.178 cm) second least size preceded by pigment type (1.163 cm) of stones. This in contrast to our study where maximum size was of mixed stones.

Not many studies regarding the association of mucosal response with weight and volume have been found in literature.

The association between average size, weight and volume of calculi with the mucosal response was found to be statistically significant ($p<0.05$). Not many studies have investigated the association of mucosal response with weight and volume of gallstones. Roa *et al*., [8] in their case control study reported that average gallstone weight, volume and density was greater in cases with carcinoma than in controls. In this study, logistic regression analysis showed that every one gm increase in stone weight, increased the likelihood of gall bladder cancer by approximately 5%, and volumes over 10 ml had an odds ratio 11 times higher than controls for developing cancer. The results were statistically significant ($p<0.05$).

Distribution of various lesions of gall bladder (n=339)

Study by Awasthi [9] reported most common pathology noted in this study was chronic cholecystitis, seen in 711 cases (97.1%). Follicular variant was seen in 22 (3.1%) cases of chronic cholecystits. Cholesterolosis, focal cholesterolosis, antral metaplasia and adenomatous hyperplasia were associated with chronic cholecytitis in 44 (6.2%), 37 (5.2%), two (0.3%) and one (0.1%) cases respectively. Active inflammation was superimposed on chronic cholecystitis in 23 (3.2%) cases. Other histomorphological lesions seen were acute cholecystitis in six (0.8%), xanthogranulomatous cholecystitis in 13 (1.8%) and empyema in two (0.3%) cases respectively. However, no malignant lesions were detected on histopathology.

Tyagi *et al*., [10] reported 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%). In 13 (6.2%) cases the diagnosis of chronic follicular cholecystitis was made [10].

Study by Verma *et al.*, had similar findings chronic cholecystitis was found in 75.6% of all cases [11].

In this present study lymphoid follicles seen in lamina propria and muscular layer were seen in 10 cases (3%), out of which one case had presence of lymphoid follicles in all the layers called follicular cholecystitis which is a variant of cholecystitis. Study by verma *et al*., observed two cases (0.2%) case of follicular cholecystitis [11].

Giri *et al*., [12] in their study reported epithelial dysplasia in six cases out of 526 cases (1.15%) of all gall bladder specimens. Yamamoto *et al*., [13] in their study reported the incidence of dysplasia in 2.2% cases. In study by Baidya *et al*., [14] epithelial dysplasia was found in 1.3% of gall bladder specimens.

In present study dysplasia was seen in five cases (1.5%).

Association of mucosal response in gall bladder with type of stone

In study Mathur *et al*., [5], in cases with cholesterol stones, most common response evoked was chronic cholecystitis (40%), followed by cholesterolosis in 18% and adenomatous hyperplasia in 15% of the cases. None of the case with carcinoma had cholesterol stone. Mixed stones were found in 7 of the 8 cases (88%) of carcinomas. No consencus has yet been made out regarding the association of the type of stone with malignancy.

Mohan *et al*., [15] observed cholesterolosis in 26.3% of cases with cholesterol stones, while carcinoma was present in 10% cases. Mohan *et al*., observed pigment stones in 7 out of 12 (58.3%) carcinoma cases while the results by Vitetta *et al*., [16] showed that primary gall bladder carcinomas were always associated with single or multiple cholesterol stones.

Our study shows the association of various mucosal responses in gall bladder with the type of stone. Chronic cholecystitis was the most common finding individually with all the three types of stones; 172 cases, 34 and 22 cases with mixed, pigment and cholesterol stones respectively which is in concurrence to study by Mathur *et al*., [5].

In the present study intestinal metaplasia was seen in seven cases which is correlated by Gopalkrishanan *et al*., [17] and mathur *et al*., [5]. In the present study intestinal metaplasia was seen equally with mixed stones and gall bladder with no stones whereas in a study by gopalkrishanan et al, intestinal metaplasia was common in gallbladders with pigment stones (11%) followed by mixed stones (6.7%). In their study intestinal metaplasia was observed in gallbladders harbouring malignancy. Intestinal metaplasia is considered as a precancerous lesion in contrast to pyloric gland metaplasia which is considered a benign lesion.

Ganpathi *et al.*, [18] have observed the de novo presentation of acalculous acute cholecystitis in several of their patients in the absence of acute illness or predisposing factors, which prompted them to undertake this study.

In a study by Kafle *et al*., [19] out of 50 cases studies, chronic cholecystitis without cholelithiasis constituted majority of histomorphological spectrum of gall bladder pathology,acute on chronic cholecystitis without stones four cases (8%), chronic cholecystitis with cholesterosis with no stones 11 cases (22%),chronic cholecystitis with no stones 25 cases (50%), follicular cholecystitis with no stones two cases (4%), chronic cholecystitis with xanthogranulomatous change, with no stones three cases (6%).

Association of various lesions – inflammation, premalignant and malignant with type of stone

Mathur *et al*., [5] in their study saw cholecystitis, hyperplasia, metaplasia and carcinoma i.e. All mucosal changes were more commonly seen with mixed stones. In carcinoma, 88% (7 out of 8 cases) had mixed stones. In cases with metaplasia, besides the 34 (58%) cases with mixed stones, 19 (32%) had combined stones. While 15 (66%) of the 24 cases of hyperplasia had mixed stones, in rest 9 cases cholesterol, combined and pigment stones appeared in equal numbers (3 each).

In the present study it is seen that cholecystitis, hyperplasia, metaplasia and carcinoma i.e. All the mucosal changes were more commonly seen with mixed stones. In cases with metaplasia, besides 5 (45.5%) cases with mixed stones, 3 (27.3%) had no stones. Dysplasia was seen in five cases out of which four (80%) associated with mixed stone and one (20%) with pigment stone. Out of four cases of carcinoma two (50%) cases were associated with mixed stones and one case with each pigment stone and no stone.

Association of various lesions – inflammation, premalignant and malignant with number of stones

In a study by Mathur *et al.*, [5] all the benign, premalignant and malignant lesions were associated more with multiple gallstones.

Vitetta *et al*., [16] and hsing *et al*., [20] saw that gall bladder cancer patients were more likely to have multiple stones. Juvonen *et al*., [21] observed that histological evidence of biliary complications are more often in patients with multiple stones than in those with solitary stones.

Domeyer *et al.*, [22] stated that the solitary gallstones were the most important predictors for severe inflammation. Khanna et al and roa et al could not document any association between the two in their respective studies.

Vitetta *et al*., [16] postulated that gall bladder carcinoma may be intimately associated with large numerous cholesterol gallstones that in the first instance may interfere with the mechanical functioning of the gall bladder. similarly, Hsing *et al*., [20] observed that gall bladder cancer patients were more likely to have multiple stones.

CONCLUSION

The histopathological spectrum of gallbladder lesions includes chronic cholecystitis and associated mucosal alterations and lesions like metaplasia, dysplasia and carcinoma. Variants of chronic cholecystitis such as xanthogranulomatous, granulomatous and follicular cholecystitis were also

noted. To conclude, it was seen that the average weight, volume and size of the gall bladder significantly correlated in increasing order with cholecystitis, hyperplasia, metaplasia and carcinoma. It shows that prompt detailed histopathological analysis of the cholecystectomy specimens will help to confirm the benign nature of the disease or to detect any precursors of malignancy. This will be decisive in the management and prognosis of the patient. Proper counselling regarding dietary modification, weight reduction and obesity management goes a long way in preventing gallstone formation and its complications.

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