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Asymptomatic gall stone disease: A clinicopathological correlation

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ABSTRACT

Introduction: The widespread use of routine ultrasound (USG) of abdomen has led to increased detection of asymptomatic gallstone disease. The cholecystectomy is the gold standard treatment for symptomatic gallstones. However, there is always a controversy regarding management of silent gallstones.

Aim: Present study designed to analyze the incidence of diverse histological changes found in gallbladder mucosa in silent gallstone diseases.

Material and methods: We evaluated the mucosal changes in 135 specimens collected from patients undergoing routine cholecystectomy for silent gallstone disease for a period of 2 years. After gross examination, the specimens were formalin fixed. Sections were taken from different areas of formalin fixed gallbladder, stained with hematoxylin and eosin and examined under light microscope.

Results: Abnormal mucosa was found in 86 (63,70%) cases of gallbladder grossly. On microscopy, chronic cholecystitis was found in 121 (89,63%) cases and xanthogranulomatous cholecystitis found in 4 cases (2,96%). Follicular cholecystitis was found in 5 (3,70%) cases. Cholesterolosis was found in 25 (18.52%) cases. Epithelial adenomatoid hyperplasia and papillary hyperplasia were found in 1 case each. Eighteen (13.33%) cases of Gastric metaplasia, 6 (4.44%) cases of intestinal metaplasia, 1 (0.74%) case of dysplasia and 2 cases (1.48%) adenocarcinoma were found.

Discussion: Silent gallstone diseases, despite being asymptomatic, always show series of mucosal changes. Data revealed metaplastic changes especially intestinal metaplasia are associated significantly with dysplastic changes.

Conclusion: Cholecystectomy should be done in all surgically fit silent gallstone cases and histopathological evaluation is important in every case to exclude metaplasia, dysplasia and carcinoma.

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1. INTRODUCTION

Gallstone disease is a major health problem globally including India.[1] Generally, it is told that bile stasis is the main factor for gallstone formation. The gallbladder functions not only to store the bile, but also to concentrate it during the inter-digestive phase by means of salt-dependent water reabsorption.[2] Gallbladder epithelium cells and biliary tract is exposed to high concentrations of potentially dangerous exogenous and endogenous compounds excreted into primary bile.[3] All columnar epithelial cells are lined by a blanket of mucus, a native physiological gel-like secretion which separates the host mucosal cells from the external milieu.[4] The gallbladder mucus plays a regulatory role in cholelithiasis as it promotes the nucleation of stones.[5] Cholelithiasis is one of the most common diseases in India with an incidence of about 4%–6%.[6] Mucus, calcium and lipids act in concert to form the gallstones.[7] Gallbladder mucin is one of the key factors in gallstone formation. However, there is little information about the diversity of mucin secretion according to the stone composition.[8] A major causative agent for stasis is gallbladder dyskinesia which in turn may be a consequence of gallbladder wall pathology.[9] However, it was observed that gallbladder tension increased, rather than decreased during the early stage of gallstone formation.[10] Cholelithiasis produces diverse histopathological changes in gallbladder mucosa namely acute inflammation, chronic inflammation, glandular hyperplasia, granulomatous inflammation, cholesterosis, dysplasia and carcinoma.[11]

Due to liberal use of USG for abdominal symptoms incidence of gallstone detection is increased manyfolds. Among all the diagnosed cholelithiasis cases, 50%–70% cases diagnosed incidentally during evaluation for other symptoms. The mucosal epithelium is high columnar with underlying lamina propria. Gallbladder mucosal changes depend on the number and type of stone, duration of disease, age and gender of the patient. Depending on the chronicity of the disease, gallstone causes varieties of mucosal changes ranging from inflammation to metaplasia and dysplasia.[12]

2. AIM

Present study designed to analyze the incidence of diverse histological changes found in gallbladder mucosa in cholecystectomy cases for asymptomatic gallstone disease for prediction of future complications in relation to age and gender of the patient that may guide for a proper management. Clinical profile and macroscopic changes in the gallbladder mucosa in patients undergoing cholecystectomy were also evaluated.

3. MATERIAL AND METHODS

This study was carried out during February 2013 to February 2015 on 135 patients undergoing cholecystectomy for asymptomatic gallstone disease. Mean duration of surgery from detection varies from 4 weeks to 10 years. Patients with high surgical risk, patients at extremes of age less than 10 years or over 80 years and patients with pregnancy were excluded from our study group. Detailed gross examination of the resected specimens with number and type of stone were studied. Parameters for gross inspection includes: appearance of serosal surface, wall thickness, mucosal texture, cystic duct. For microscopy, the specimens were fixed in 10% formalin and sections were taken from body, fundus, neck and abnormal looking sites. They were stained in haematoxylin and eosin stain and seen under light microscope. The different microscopic changes like inflammation, hyperplasia, cholesterolosis, metaplasia, dysplasia and CIS were studied.

Table 1. Patient demographic data.

Age of patient	Mean age 45 years (10–76 years)
Male	60
Female	75
Mean duration of sugey Since detection	16 weeks (3 days to 12 years)
Single stone	45
Multiple stones	90

Table 2. Type of stone.

Type of stone	Single	Multiple	Total
Cholesterol	17	23	40
Pigment	18	17	35
Mixed	10	50	60
Total	45	90	135

Comments: 2 P value = 0.001.

Table 3. Operative findings /Gross features.

Macroscoping finding	Features	Number	Percentage (%)
Serosal surface	Normal	106	78.5
	Congested	29	21.5
Wall	Normal	17	12.6
	Thin walled	97	71.9
	Thick walled	16	11.9
	Focal thickening	5	3.7
Mucosa	Normal	49	36.3
	Ulcerated	11	8.1
	Haemorrhagic	7	5.2
	Atrophic	54	40.0
	Nodular	14	10.4
Cystic duct	Stone impacted	4	3.0
	Wide cystic duct	4	3.0

4. RESULTS

Out of 135 cases 60 were male and 75 female. Though the number of affected female was more as compared to male but it is not significant ($P = 0.085$). Mean age of presentation was 45 years (10–76 years). Multiple stones were found in 90 cases and single stone in 45 cases (Table 1). Most common type of stone found was mixed type in 60 (44.4%) cases, followed by cholesterol stone in 40 (29.6%) cases and pigment stone in 35 (25.9%) cases (Table 2). On gross examination serosal surface was found normal in 106 (78.5%) cases and congested in only 29 (22.5%) cases. The wall thickness found normal (3 mm) in 17 (12.6%) cases, thin walled (<3 mm) in 97 (71.9%) cases, thickened in 16 (11.9%) cases and focal thickening was found in 5 (3.7%) cases. Impacted stone in cystic duct was found in 4 (3.0%) cases, wide cystic duct in 4 (3.0%) cases and rest were found normal. On macroscopic examination of mucosa, it was found normal in 49 (36.3%) cases, ulcerated in 11 (8.1%) cases, haemorrhagic in 7 (5.2%)

Table 4. Microscopic changes with gender*.

Changes	Male	Female	Total
Chronic cholecystitis	38	83	121
Eosinophilic cholecystitis	0	1	1
Follicular cholecystitis	2	3	5
Xanthogranulomatous cholecystitis	1	3	4
Cholesterosis	10	15	25
Papillary hyperplasia	10	13	23
Adenomatous hyperplasia	0	1	1
Gastric metaplasia	7	11	18
Intestinal metaplasia	2	6	8
Dysplasia	0	1	1
Adeno ca	1	1	2
Total			

Comments: * T test: $P = 0.226638$.

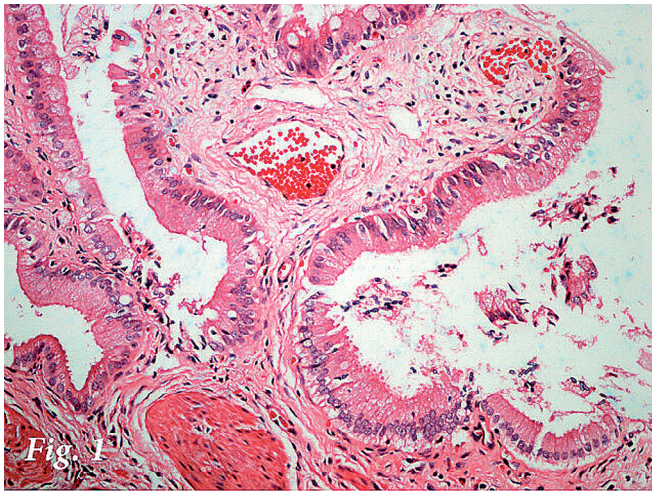

Figure 1. Chronic cholecystitis: Chronically inflammed mucosa with lympho-plasmacytic infiltrate in the wall.

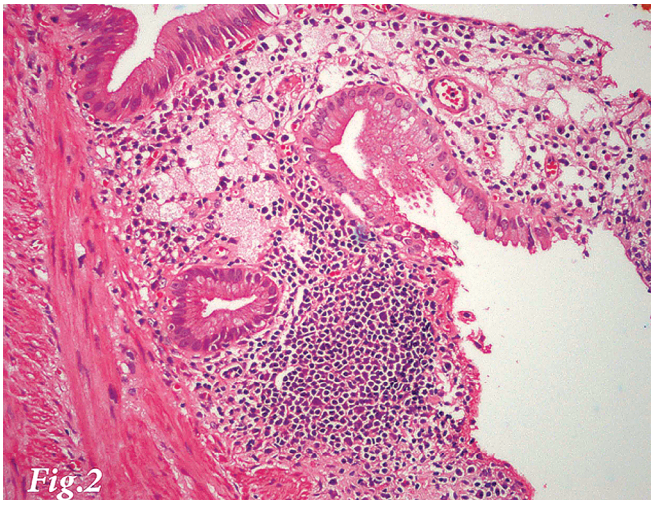

Figure 2. Cholestesterosis: Sheets of foamy macrophages infiltration in the lamina propria.

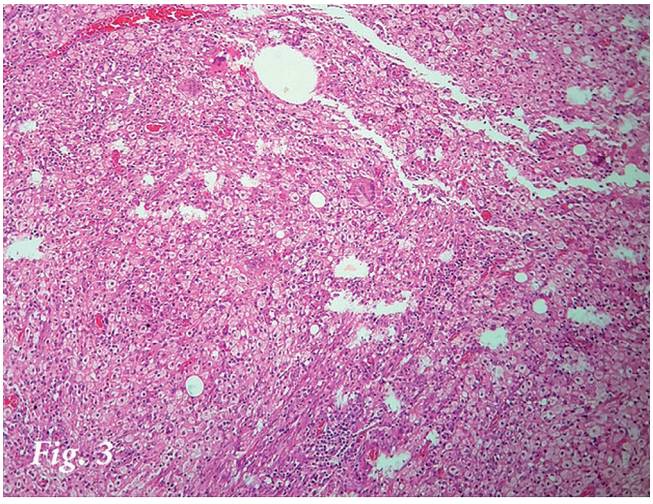

Figure 3. Xanthogranulomatouscholecystitis: Wall of the gallbladder infiltrated with sheets of foamy histiocytes, lymphocytes, plasma cells and multinucleated giant cells.

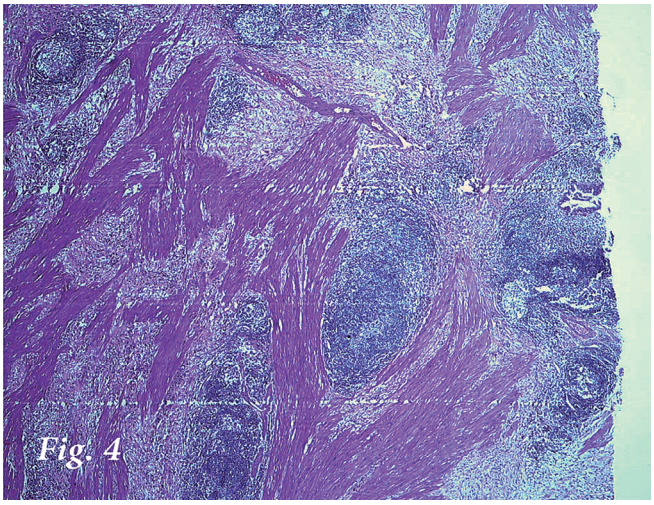

Figure 4. Lymphocytic cholecystitis: Wall of the gallbladder shows multiple lymphoid follicle formation.

Table 5. Mucosal changes according to age group.

Changes	Age groups							
	10–19	20–29	30–39	40–49	50–59	60–69	70–79	Total
Chronic cholecystitis	5	28	26	18	25	15	7	124
Eosinophilic cholecystitis	0	0	0	1	0	0	0	1
Follicular cholecystitis	0	0	2	1	1	1	0	5
Xanthogranulomatous cholecystitis	0	0	0	1	2	1	0	4
Cholesterosis	0	2	4	6	8	3	2	25
Papillary hyperplasia	0	0	1	3	5	6	8	23
Adenomatous hyperplasia	0	0	0	1	0	0	0	1
Gastric metaplasia	0	3	6	5	2	1	1	18
Intestinal metaplasia	0	0	1	1	3	3	0	8
Dysplasia	0	0	0	0	0	1	0	1
Adeno ca	0	0	0	0	1	1	0	2
Total	5	33	40	37	47	32	18	212

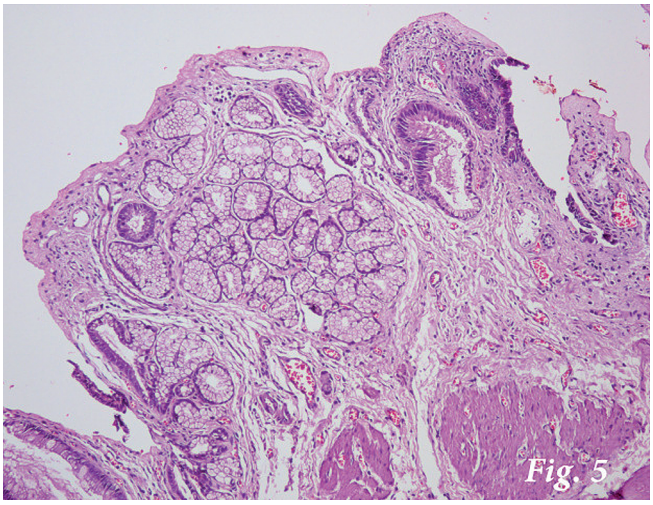

Figure 5. Gastric metaplasia: Mucosa showing lobules of pyloric gland.

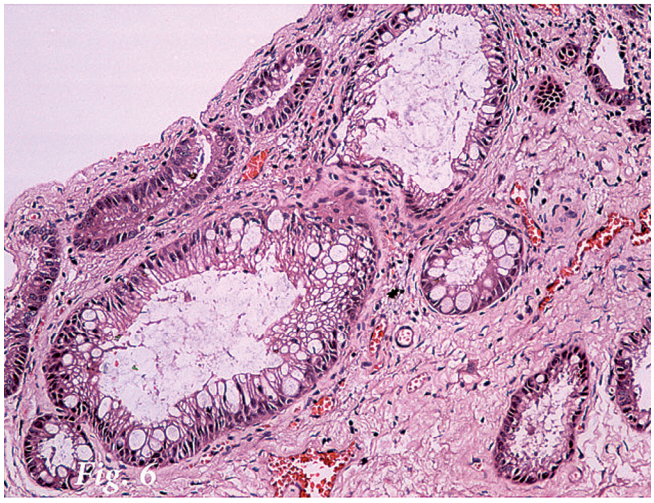

Figure 6. Intestinal metaplasia: Intestinal type glands with goblet cell metaplasia.

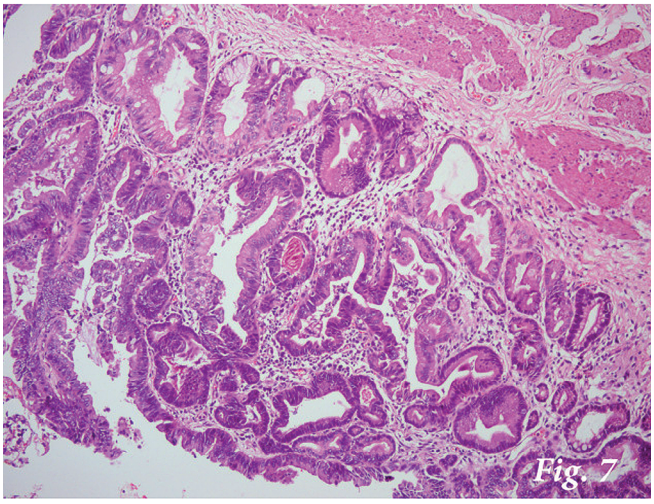

Figure 7. Dysplasia: Glands showing high grade dysplasia limited to mucousa.

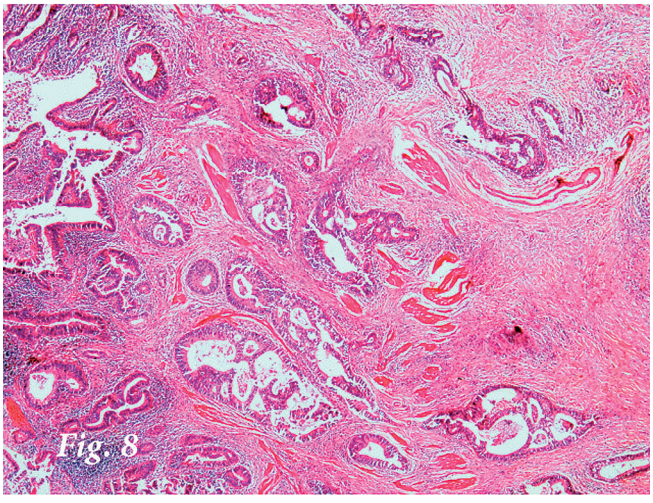

Figure 8. Adenocarcinoma: Infiltrative neoplastic glands in the lamina propria and muscularis propria.

cases, atrophic in 54 (40.0%) cases and nodular in 14 (10.4%) cases (Table 3). On microscopic examination, chronic cholecystitis reported in 121 (89.6%) cases (Figure 1). Twenty five (18.5%) cases of cholesterolosis (Figure 2), 4 (3.0%) cases of xanthogranulomatous cholecystitis (Figure 3), 1 (0.7%) case of eosinophilic cholecystitis and 5 (3.7%) cases of follicular cholecystitis (Figure 4) were noted. In hyperplasia of mucosa, adenomatous hyperplasia in 1 (0.7%) case and papillary hyperplasia in 23 (17.0%) cases were seen. Gastric metaplasia (Figure 5) was reported in 18 (13.3%) cases, intestinal metaplasia (Figure 6) in 6 (4.4%) cases, dysplasia (Figure 7) in 1 (0.7%) case and adenocarcinoma (Figure 8) in 2 (1.5%) cases (Table 4). Analyzing the age gradient, papillary hyperplasia, gastric metaplasia and intestinal metaplasia were found in age group of 50–79, 30–49 and 50–69 years respectively. Dysplasia and adenocarcinoma were found in 60–69 years age group (Table 5).

5. DISCUSSION

Cholelithiasis causes injury to mucosa and leads to a series of changes ranging from inflammation, hyperplasia, cholesterolosis[13] and precancerous condition like metaplasia, dysplasia and neoplastic lesions.[14] It is the most common cause of gallbladder cancer worldwide.[15] In the present study, we have taken patients undergoing cholecystectomy for asymptomatic gallstones. Their age ranges 10–79 years. Maximum cases are in the age group of 5th decade (23.7%) followed by 4th (21.5%) and 3rd decade (19.2%). Mean age in the present study is 45 years where as in study by Sood et al. and Banarjee et al. it was 43.5 years and 39.5 years, respectively. Male to female ratio is 1 : 1.25 where as in other studies it ranges from 1 : 3.2 to 1 : 6.5.[16] This may be due to type of patient and regional variation. In present study chronic inflammation was the most common finding found in 90% cases. This coincides with the study by Sood et al. where they found 92% cases were having chronic cholecystitis. Features of acute cholecystitis was not found in our study where as study by Vahini et al. (2015) showed 18.3% cases having acute cholecystits.[17] This can be explained on basis of patient selection criteria and their duration between diagnosis and resection of gallbladder. We found eosinophillic cholecystitis in 1 (0.7%) case which is similar to a study by Kaur et al. (0.78%) and Vahini et al. (0.9%). Many hypotheses proposed for eosinophilic cholecystitis[18] but in our case it may be idiopathic. Xanthogranulomatous cholecystitis was found in 4 (3.0%) cases. Non-neoplastic lesions were found in 80% cases and maximum cases (66.6%) were associated with multiple stone. Similar result was found by Goyal et al. (2014)[6] who showed multiple stones are more common than single stone (72%).[19] Mixed stone was the most common type of stone (44.4%) in our study. Cholesterol and pigment stones were found in 29.6% and 25.9% cases, respectively. In present study we found metaplasia associated with chronic cholecystitis in 19% cases. Out of which antral metaplasia and intestinal metaplasia are 13% and 6%, respectively. In contrast, a data given by Mukhapadhyay and Landas[20] where antral and intestinal metaplasia were 59.5% and 9.8%, respectively. They have demonstrated the age gradient in progression of disease from antral-type metaplasia to intestinal metaplasia to dysplasia.[20] Similar age gradients were seen in our study. We found antral type metaplasia more common in age group 30–50 years, intestinal metaplasia in 50–69 years age group and dysplasia in 60–69 years age group. However, incidence of dysplasia alone was very low (0.7%) compared to simillar studies. Albores-Saavedra et al. found dysplasia in 13.5% of Mexican patients and Duarte et al. also reported similar findings (13.6%) from Chile. This differences in incidence of dysplasia in our case series can be explained by factors like smaller sample size, inter-observer variation of precursor lesions and the most importantly geographic and racial differences. Adenocarcinoma was found in 2 (1.5%) cases above 60 years. Occurence of gallbladder cancer is more related to duration of gallstone disease not to age of patient.[20] A study by Behari et al. shows after 13 years of follow up in asymptomatic case and only 0.2% of them diagnosed to have cancer.[21] According to some autopsy studies only 1%–4% of patients with cholelithhiasis developed cancer compared to those not containing gall stone. Treatment of silent gallstone disease is still a mater of confusion to surgeons. Shukla et al. reported highest incidence of gallbladder carcinoma in the world in Indo-Gangetic belt of India.[22]

6. CONCLUSIONS

As explained by present study there is an age gradient change from inflammatory pathology to metaplasia and then dysplasia. The incidences of malignant and premalignant cases are increasingly being detected. Therefore, in all cases of silent gallstone disease, gallbladder should be resected if patient condition permits.

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