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Evaluation of gallbladder mucosal changes about the type of stones in patients undergoing open cholecystectomy: A study of 184 patients

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ABSTRACT

Background: Cholelithiasis is 7 times more frequent in North India, with an overall incidence of about 2–29%. The number and different morphology of gallstones can cause alterations in the gallbladder (GB) mucosa. GB mucosal change depends on the duration of cholelithiasis, size, number, type of stone, and the gender of the patient. The coexistence of gallstones with cholecystitis, hyperplasia, intestinal metaplasia, and carcinoma is well known in the literature. Incidental gallbladder (GB) carcinoma is revealed in 1% of all cholecystectomies done for benign conditions. The pathological stage of the disease decides the prognosis of the disease. **Aims and Objectives:** Gallstones are known to produce various histopathological changes in the GB. We aim to correlate gallstone characteristics such as (number and morphological type) with the type of mucosal response in the GB (inflammation, hyperplasia, metaplasia, and carcinoma). **Materials and Methods:** A study of gallstones was done in 184 cases of open cholecystectomies based on the histological changes. One hundred and sixty-five (89.95%) were associated with gallstones, and the rest 19 cases (10.05%) were of acalculous cholecystitis. The changes in the mucosa of the calculous GB (165 cases) were studied, and the correlation between the mucosal changes and the number and type of stones was evaluated. Tissue sections for histopathological studies were taken from the fundus, body, neck, and abnormal-looking areas of the GB. **Results:** A gender study revealed a higher incidence of inflammatory changes in males, while GB hyperplasia, intestinal metaplasia, and cancer were found only in females. **Conclusion:** Correlation of mucosal changes with a number, duration of disease, and morphological type of stones has suggested that there could be an association with the various GB mucosal changes such as inflammation, hyperplasia, metaplasia, and carcinoma of the GB.

Key words: Carcinoma; Gallbladder; Intestinal metaplasia

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INTRODUCTION

Cholelithiasis is 7 times more frequent in North India, with an overall incidence of about 2–29%.[1] The number and different morphology of gallstones can cause alterations in the gallbladder (GB) mucosa. GB mucosal change depends on the duration of cholelithiasis, size, number, type of stone, and the gender of the patient.[2] The coexistence of gallstones with cholecystitis, hyperplasia, intestinal metaplasia, and carcinoma is well known in the literature.[3] Incidental GB carcinoma is revealed in 1% of all cholecystectomies done for benign conditions.[4] The pathological stage of the disease decides the prognosis of the disease. GB metaplasia is characterized by intestinal or pyloric-type epithelium found in association with cholelithiasis.[5] Histopathological changes can predict the chances of GB cancer formation. The etiology and pathogenesis of GB cancer are not well known. The main complexity in studying the precursor lesions of this disease is that it is unfeasible to perform follow-up because the diagnosis is recognized during surgery or after the cholecystectomy. Therefore, the proof relating these lesions

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to the cancer is decided indirectly. A better understanding of the various risk factors and premalignant lesions of the GB could help select prophylactic cholecystectomies and thus reduce mortality.[6] Due to the above reasons, mucosal changes in the GB due to stones were studied in the present study.

Aims and objectives

Gallstones are known to produce various histopathological changes in the GB. We aim to correlate gallstone characteristics such as (number and morphological type) with the type of mucosal response in the GB (inflammation, hyperplasia, metaplasia and carcinoma). GB cancer is an uncommon but highly fatal malignancy; around 10% of new cases are diagnosed in India. Due to its progressive nature, GB cancer has a poor prognosis. A better understanding of risk factors that leads to its development could help improve the management options. The presence of stones in the GB generates varied mucosal reactions, which results in different types of histopathological changes in the mucosa. We aim to correlate various mucosal responses such as inflammation, hyperplasia, metaplasia, and carcinoma to different gallstones characteristics (such as number and morphology type).

MATERIALS AND METHODS

The study was carried out in General Surgery Department of ESIC Medical College and Hospital, Faridabad, Haryana, India, between January 2018 and December 2019, and a total of 184 patients who underwent open cholecystectomies were evaluated. The study was pre-approved by the Institutional Ethics Committee for the final permission. Out of 184, 89.95% (165) were associated with gallstones, and the rest 10% (19) of cases were of acalculous cholecystitis. We studied the changes in the mucosa of calculous GB 90% (165 cases). The stones were evaluated for various parameters; (1) number: Single/multiple and (2) morphological type: Cholesterol/pigmented/combined/mixed.

A pathologist did the histopathological examination. Four sections, two from the body and one from the fundus and neck of the GB, were taken. The different sections were taken from abnormal appearing mucosa for histopathological examination. Sections were stained with hematoxylin and eosin stain.

An abdominal ultrasound examination was done to diagnose cholecystolithiasis in all the patients. GB changes suggestive of GB cancer were not confirmed in any patients during the pre-operative stage. The age of patients ranged from 12 to 89 years. The surgeon did a gross examination of the removed GB on the operation table in all patients. The tissue was then sent for histopathological examination.

The pattern of response in GB mucosa such as inflammation (acute cholecystitis and chronic cholecystitis), empyema (abscess), xanthogranulomatous cholecystitis, hyperplasia, intestinal metaplasia, dysplasia, and malignant changes was studied about number and morphological type of stones.

RESULTS

A total of 184 consecutive specimens of cholecystectomy were examined, out of which 165 (90%) were associated with gallstones, and the rest 19 cases (10%) were of acalculous cholecystitis. We studied the changes in the mucosa of the GB (165 cases) and tried to find out whether any correlation existed between the mucosal changes and the number and type of stones. Out of 165 patients, 33 were male and 132 were female with an M: F ratio of 1:4 (Table 1).

The mixed type of stone was the most frequently encountered stone present in 115 cases (70%), predominantly multiple in numbers, followed by pigmented type around 33 cases (20%). Cholesterol stones were present in only 17 cases (10.30%). A total of 120 patients had multiple stones, while 45 patients had single stones (Table 2).

Table 1: Relation of various mucosal changes with gender

Type of lesion	Male	Female	Total	P-value (Using independent t-test)
Chronic cholecystitis	24	118	142	11.5%, marginally significant
Acute cholecystitis	4	0	4	
Cholesterolosis	1	3	4	
Follicular cholecystitis	0	0	0	
Xanthogranulomatous cholecystitis	3	4	7	
Papillary hyperplasia	0	1	1	
Adenomatoid hyperplasia	0	1	1	
Gastric metaplasia	0	1	1	
Intestinal metaplasia	1	3	4	
Carcinoma	0	1	1	

Table 2: Correlation between morphological types and number of stones

Number of stones				P-value (Using independent T-test)
Type of stone	Single	Multiple	Total	
Cholesterol	9	8	17	21.1%, insignificant
Mixed	20	95	115	
Pigmented	16	17	33	

The most common GB change seen was chronic cholecystitis with cholelithiasis (142 cases, 86%). Xanthogranulomatous cholecystitis was present in 7 cases (4%). Chronic cholecystitis with metaplasia was present in 5 cases (3%) followed by chronic cholecystitis with focal cholesterol is in 4 cases (2.4%). GB carcinoma was found in 1 case (0.6%) (Table 3).

While comparing the mucosal changes with the number of stones, it was found that almost all the lesions were more common in the GB with the multiple numbers of stones (may be due to the presence of multiple stones is far more common than the single [72%] or may be due to more irritation of mucosa with a higher number of stones). Multiple stones were more commonly associated with cholecystitis, xanthogranulomatous cholecystitis, and metaplasia (both gastric and intestinal) (Table 4).

DISCUSSION

In North India, gallstones are 7 times more common, with an overall incidence of about 2.29%. A retrospective study of 165 patients was carried out to determine the correlation between gallstones and GB mucosal changes.

It is a known fact that a relationship does exist between cholecystolithiasis and GB cancer, as gallstones are found in 80% of all GB cancer cases.[6] In one study, the occurrence of GB cancer is about 1.68%, whereas it is about 3.5% in another study. In this study, multiple histopathological sections of GB were examined. The coexistence of cholecystolithiasis with xanthogranulomatous cholecystitis, adenomyomatosis, and pyloric and intestinal metaplasia is well known in literature.[7] In our study, the age range was from 12 to 89 years. The majority of patients were in between 30 and 39 years. The main sufferers were female, with the male: female ratio being 1:4, an incidence similar to other studies.[1,8]

Mixed stones incidence 70% (115/165) are the most commonly encountered variety of gallstones in North India as in our study.[1,9] The incidence of pigmented stones was 20% (33/165) and that of cholesterol stones was 10.30% (17/165); single stones were in 45/165 (27.27%). Multiple stones were in 120/165 (72.72%) patients in other reports.[6,10,11] This points out that cases having multiple stones are more symptomatic (cholecystitis) than with single stone. The mucosal changes such as hyperplasia, metaplasia, and carcinoma were also more common in cases with multiple mixed types of stone (Figures 1-3).

Table 3: Various types of mucosal changes about the number of stones

	Number of stones			P-value (Using independent t-test)
Type of lesion	Single	Multiple	Total cases	
Chronic cholecystitis	41	101	142	11.5% – marginally significant
Acute cholecystitis	0	4	4	
Cholesterolosis	1	3	4	
Follicular cholecystitis	0	0	0	
Xanthogranulomatous cholecystitis	2	5	7	
Papillary hyperplasia	0	1	1	
Adenomatoid hyperplasia	0	1	1	
Gastric metaplasia	0	1	1	
Intestinal metaplasia	1	3	4	
Carcinoma	0	1	1	

Table 4: Correlation of mucosal changes with the morphology of stones

Type of lesion	Type of stones			Total
	Cholesterol	Mixed	Pigmented	
Chronic cholecystitis	17	103	22	142
Acute cholecystitis	0	1	3	4
Cholesterolosis	0	1	3	4
Follicular cholecystitis	0	0	0	0
Xanthogranulomatous cholecystitis	0	5	2	7
Papillary hyperplasia	0	0	1	1
Adenomatoid hyperplasia	0	1	0	1
Gastric metaplasia	0	0	1	1
Intestinal metaplasia	0	3	1	4
Carcinoma	0	1	0	1
P-value (determined by independent t-test)		← → 13.8%-insignificant		
		16.8%-insignificant ← →		
		← → 0.6%- Extremely significant		

Precancerous GB mucosal changes have got clinical as well as pathological significance. However, a pathologist frequently overlooks these changes.[12] In our study, GB mucosal hyperplasia was found in 2/165 (1.2%) cases. When multiple sections of the GB such as fundus, body, and neck were scrutinized properly, dysplasia and carcinoma in situ were detected in 5/165 (3%) and 1/165 (0.6%) female patients.

The presence of stones leads to mechanical mucosal irritation, which results in the hyperplasia of the GB. Intestinal metaplasia was encountered in only 4/165 cases (2.4%). Out of 165 cases of cholelithiasis, GB carcinoma was encountered in 0.6% (1/165). The higher incidence of cholecystolithiasis partially explains the increased risk of GB cancer in women than men, as female hormones also play a role in the etiology of gallstones. Higher and extended contact to female sex hormones may be the main factor. This may be due to reduced activity of cholesterol reductase and an increase in the activity of HMG-CoA reductase with age, resulting in enhanced cholesterol secretion and saturation of bile. The female sex hormones may play a role to expose them to factors that possibly promote the formation of gallstones. Therefore, early menarche, early first and multiple pregnancies, and delayed menopause result in extended hormonal exposure and thus may augment the risk of GB carcinoma.[6]

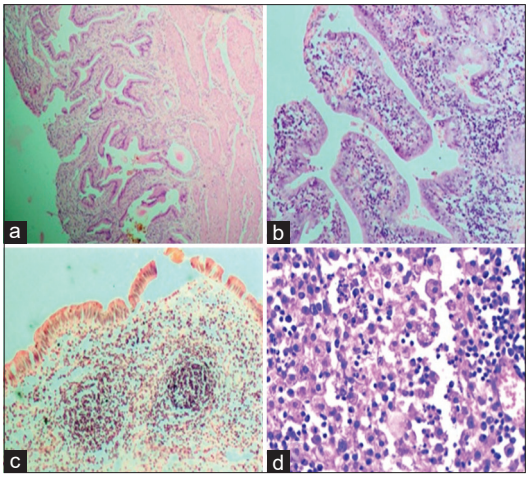

Figure 1: Photomicrographs showing (a) Rokitansky-Aschoff sinuses characteristic of chronic cholecystitis; (b) acute on chronic cholecystitis; (c) follicular cholecystitis; (d) foamy macrophages admixed with mononuclear inflammatory infiltrate seen in xanthogranulomatous cholecystitis (H&E)

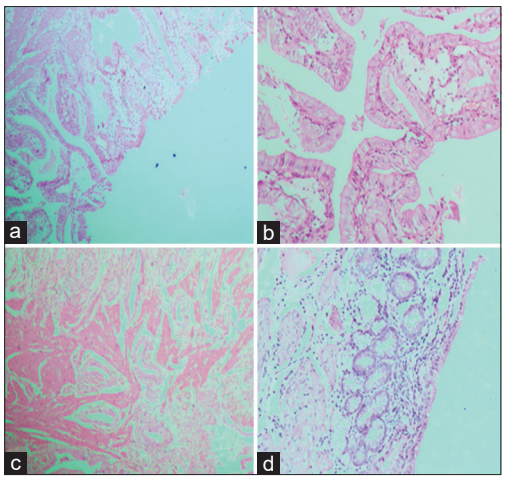

Figure 2: Photomicrograph showing (a) cholesterolosis in low power; (b) high-power view of cholesterolosis showing lipid-laden macrophages; (c) adenomyomatosis of GB; (d) pyloric metaplasia GB (H&E)

GB metaplasia changes were common in patients with multiple mixed stones as in other studies.[13] This association seems to be relative, and a statistical association could not be demonstrated between several stones and mucosal response.[14]

Xanthogranulomatous cholecystitis is an unusual inflammatory and destructive GB process that can spread to adjacent structures and confuse cancer. This histological alteration occurs in approximately 2.9% of all cholecystectomies, affects men and women equally, and is frequently associated with gallstones. The incidence of cancer in GBs associated with xanthogranulomatous cholecystitis is about 9–12%. Similarly, xanthogranulomatous cholecystitis incidence is high among elderly females.

In the present study, acute cholecystitis is higher in males, as in other studies.[15] With advancing age, the occurrence of cholecystolithiasis and GB cancer increases. An

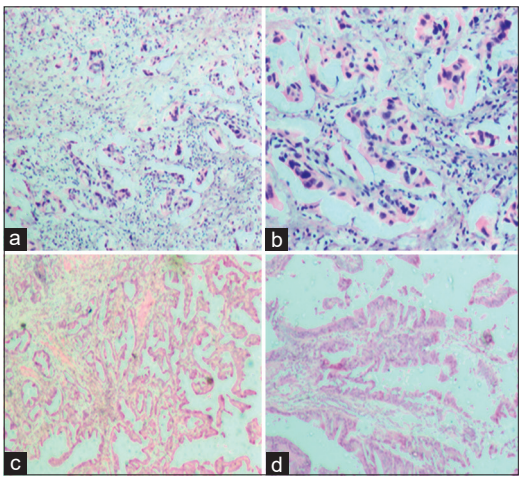

Figure 3: Photomicrograph showing (a) low-power view of adenocarcinoma GB; (b) high-power view shows attempted gland formation with moderate pleomorphism – moderately differentiated adenocarcinoma GB; (c) low-power view of papillary carcinoma GB; (d) high-power view showing papillae with fibrovascular cores lined by malignant cells – papillary carcinoma GB (H&E)

estimated 0.25% of the patients over the age of 65 with cholecystolithiasis may develop GB carcinoma, which is related to the duration of gallstone disease rather than the age of patients.[16] In our study, there were 1/165 cases of GB carcinoma. Adenomatoid hyperplasia, a non-inflammatory benign GB alteration, mostly occurs in middle-aged patients, and its occurrence increases with age. It is presently recognized as a precancerous lesion, and cancer cases associated with areas of adenomyomatosis have been reported in the literature.[17]

In our study, the incidence of metaplasia and dysplasia increased with age, and the metaplastic alterations and dysplasia are taken as precancerous lesions. As GB cancer is an extremely slow progressive disease, a prolonged follow-up may be needed.[10] Gracie and Ransohoff[18] did a follow-up on asymptomatic cholecystolithiasis (123 patients) for 7 years without the occurrence of GB cancer.

Whether prophylactic cholecystectomy should be done in asymptomatic gallstones are still debatable. However, an Indian study[19] has recommended that prophylactic cholecystectomies should be done for asymptomatic gallstones in young patients with a high incidence of GB cancer with the following changes: (i) With thickened GB wall (>3 mm), (ii) with large gallstones (>3 cm), (iii) patients with porcelain GB, and (iv) sessile polyps (>1 cm).

The results of this study maintain that there could be an association between GB stones and GB histological changes. However, further work is needed to understand about various risk factors for GB cancer. This understanding is crucial to establish surgical treatment for the various pathological GB conditions, such as symptomatic or asymptomatic calculous cholecystitis.

Limitations of the study

Further studies are needed to understand GB stones carcinogenesis and its risk factors.

CONCLUSION

This study suggests that patients with multiple gallstones are more symptomatic (cholecystitis) than with a single stone. The mucosal changes such as hyperplasia, metaplasia, and carcinoma were also common in patients with multiple mixed types of stones.

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Authors Contribution:
VS- Concept and design of the study, prepared first draft of manuscript, coordination, statistical analysis, and interpretation; **RK**- Reviewed the literature and manuscript preparation; **JP**- Revision of the manuscript; **VT**- Revision of the manuscript and **SG**- Concept and design of the study

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