Original Article

Correlation between gallstones characteristics and gallbladder mucosal changes: A retrospective study of 313 patients

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ABSTRACT

Background and Aim: Gallbladder (GB) cancer has poor prognosis as it progresses very fast. Etiology or pathogenesis of GB cancer is still obscure and very little is known about it. A better understanding of risk factors that lead to its development could help improve the management options. Presence of stones in GB generates varied mucosal reaction which results in different types of histopathological changes. Our aim was to correlate the various types of mucosal response like inflammation, hyperplasia, metaplasia, and carcinoma to different gall stones characteristics (like number and morphology type). **Materials and Methods:** A retrospective study of 346 cases of removed GB was done which was based on the histological changes. A total of 313 (90%) were associated with gallstones and the rest 33 cases (10%) were of acalculous cholecystitis. The changes in mucosa of calculous GB (313 cases) were studied and correlation between the mucosal changes and the number and type of stones was evaluated. Varied parameters of gall stones like number and morphological type were studied. Tissue section for histopathological studies was taken from fundus, body, neck, and from abnormal looking areas while doing grossing. **Results:** Gender study revealed a higher incidence of inflammatory changes in males, while GB hyperplasia, intestinal metaplasia, and cancer were only found in females. A progressive increase in the average age was noticed fromintestinal metaplasia to carcinoma, suggesting that the metaplasia-carcinoma succession may occur in GB cancer. **Conclusion:** Correlation of mucosal changes with size and morphological type of stones has suggested that there could be an association between some histological alterations of GB and cancer.

Key words: Carcinoma, gallbladder, intestinal metaplasia

INTRODUCTION

Cholelithiasis is seven times more common in North India with an overall incidence of about 2.29%. Number and different morphology of gallstones cause alteration in GB mucosa. GB mucosal change depends upon the duration of cholelithiasis and also on the gender of patient. Coexistence of gallstones with cholecystitis, hyperplasia, intestinal metaplasia, and carcinoma is well-known in literature. Incidental gallbladder (GB) carcinoma is revealed in 0.3-2% of all cholecystectomies done for benign conditions. Pathological stage of the disease decides the prognosis of disease. GB metaplasia is characterized by intestinal or pyloric-type epithelium found in association with cholelithiasis.[1] Histopathological changes can predict the increased chances of GB cancer. GB cancer is the fifth most common cancer of the gastrointestinal tract.[2,3] It is a disease known for its fast growth and high mortality rate. Etiology and pathogenesis of GB cancer is not well-known. The main difficulty in studying the precursor lesions of this disease is the fact that it is impossible to perform follow-up, because the diagnosis is established during surgery or after the cholecystectomy. Therefore, the evidence relating these lesions to the cancer is determined indirectly. A better understanding of the risk factors for GB cancer and premalignant lesions of the GB could help in selection of prophylactic cholecystectomies and thus reduction in mortality.[4] Due to above reason, mucosal changes in GB due to stones were studied.

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MATERIALS AND METHODS

A retrospective study was carried out in a rural medical college between Jan 2012 and Feb 2013 and total 346 patients who underwent cholecystectomies were evaluated. Out of 346, 90% (313) were associated with gallstones and the rest 10% (33) cases were of acalculous cholecystitis. We studied the changes in mucosa of calculous gall bladder (313 cases). The stones were evaluated for variousparameters; 1) number: Single/multiple, 2) morphological type: Cholesterol/pigmented/combined/mixed. The histopathological examination was done by a single senior pathologist. Four sections; two from body and one each from the fundus and neck of GB were taken. Additional sections were taken from abnormal appearing mucosa. Sections were stained with hematoxylin and eosin stain [Figure 1].

An abdominal ultrasound examination was used to diagnose cholecystolithiasis in all the patients. GB changes suggestive of GB cancer were not confirmed in any of the patients during the preoperative stage.

Age of patients ranged from 12 to 89 years. In all patients, the surgeon did a macroscopic examination of the removed GB on the operation table. Tissue was sent for histopathological examination.

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

RESULTS

A total of 346 consecutive specimens of cholecystectomy were examined, out of which 313 (90%) were associated with gallstones and the rest 33 cases (10%) were of acalculous cholecystitis. We studied the changes in mucosa of calculous gall bladder (313 cases) and tried to find out if any correlation existed between the mucosal changes and the number and type of stone. Out of total 313 patients, 60 were males and 253 were females with an M: F ratio of 1:4.2. Maximum number of patients was in the age group of 30-39 years. The youngest patient was a 12 year-old-male, while the oldest was a female. Maximum females suffered were between 30 and 49 years age group, whereas maximum male suffered were 50-69 years age group [Tables 1 and 2].

Incidence of acute cholecystitis higher in male patients as compared with female patients.

Incidence of metaplasia is higher in elderly female patients. Patients suffering with metaplasia are younger than patients suffering with GB cancer and age difference is about 10-15 years [Table 3].

Mixed type of stone was the most frequently encountered stone present in 213 cases (68%), which was predominantly multiple in numbers; followed by combined type which in most cases was single in number. Pigment and cholesterol stones were present in only 18 and 17 cases, respectively. A total of 218 patients had multiple stones, while 95 patients had single stone [Table 4].

On studying the gall bladder mucosa microscopically, the most common change observed was chronic cholecystitis (181 cases, 58%). Gastric metaplasia was the second most common finding along with chronic cholecystitis, present in 31 cases (10%), followed by acute on chronic inflammation and intestinal metaplasia with 30 cases each [Table 5].

While correlating the mucosal changes with the number of stones, it was found that almost all the lesions were more common in GB with multiple number of stones (may be owing to the factor that multiple stones are far more common than single (72%) except papillary hyperplasia

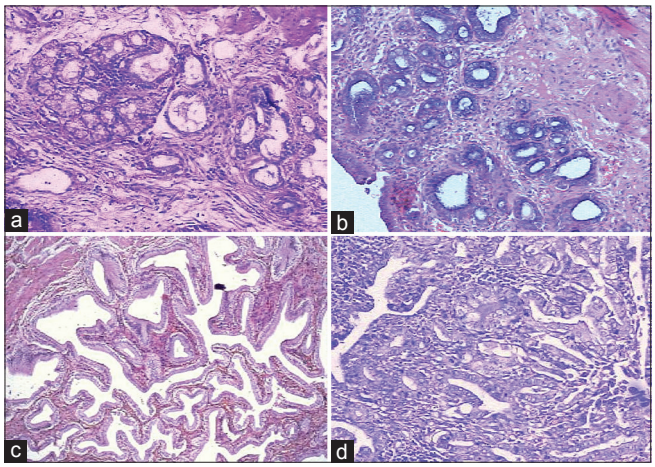

Figure 1: Microscopic picture of gall bladder wall revealing (a) Gastric metaplasia (H and E, ×40), (b) Intestinal metaplasia (H and E, ×40), (c) Papillary hyperplasia (H and E, ×10), and (d) Adenocarcinoma (H and E, ×40)

Table 1: Relation various mucosal changes with gender

Type of lesion	Male	Female	Total
Chronic cholecystitis	14	167	181
Acute cholecystitis	23	7	30
Cholesterolosis	1	10	11
Eosinophiliccholecysitis	0	1	1
Follicular cholecystitis	1	4	5
Xanthogranulomatouscholecystitis	2	6	8
Gangrenous cholecystitis	0	1	1
Papillary hyperplasia	1	6	7
Adenomatoid hyperplasia	2	2	4
Gastric metaplasia	9	22	31
Intestinal metaplasia	7	23	30
Carcinoma	0	4	4
Total cases	60	253	313

Table 2: Various gallbladdermucosa changes according to various age groups

Type of lesion	Age								
	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	Total cases
Chronic cholecystitis	4	35	41	35	27	32	6	0	181
Acute cholecystitis	0	0	2	3	13	10	2	0	30
Cholesterolosis	0	2	3	4	2	0	0	0	11
Eosinophiliccholecysitis	0	0	0	0	1	0	0	0	1
Follicular cholecystitis	0	1	0	2	1	1	0	0	5
Xanthogranulomatouscholecystitis	0	0	0	2	4	1	1	0	8
Gangrenous cholecystitis	0	0	0	0	0	0	1	0	1
Papillary hyperplasia	0	0	0	0	2	2	3	0	7
Adenomatoid hyperplasia	0	0	0	0	0	1	3	0	4
Gastric metaplasia	0	0	0	7	12	6	6	1	31
Intestinal metaplasia	0	0	0	8	15	3	4	0	30
Carcinoma	0	0	0	0	0	2	2	0	4
Total cases	6	50	67	63	52	57	17	1	313

Table 3: Correlation between morphological types and number of stones

Type of stone	No. of stones		
	Single	Multiple	Total
Cholesterol	17	0	17
Combined	50	15	65
Mixed	22	191	213
Pigment	6	12	18
Total	95	218	313

Table 4: Various types of mucosal changes

Type of lesion	Total cases
Chronic cholecystitis	181
Acute cholecystitis	30
Cholesterolosis	11
Eosinophiliccholecystitis	1
Follicular cholecystitis	5
Xanthogranulomatouscholecystitis	8
Gangrenous cholecystitis	1
Papillary hyperplasia	7
Adenomatoid hyperplasia	4
Gastric metaplasia	31
Intestinal metaplasia	30
Carcinoma	4
Total cases	313

Table 5: Various types of mucosal changes in relation to number of stones

Type of lesion	Number of stones		
	Single (%)	Multiple (%)	Total cases
Chronic cholecystitis	49 (27)	132 (73)	181
Acute on chronic cholecystitis	12 (40)	18 (60)	30
Cholesterolosis	3 (27)	8 (73)	11
Eosinophiliccholecystitis	0 (0)	1 (100)	1
Follicular cholecystitis	1 (20)	4 (80)	5
Xanthogranulomatouscholecystitis	1 (12.5)	7 (87.5)	8
Gangrenous cholecystitis	0 (0)	1 (100)	1
Papillary hyperplasia	5 (71)	2 (29)	7
Adenomatoid hyperplasia	1 (25)	3 (75)	4
Gastric metaplasia	8 (25)	23 (75)	31
Intestinal metaplasia	8 (27)	22 (73)	30
Carcinoma	1 (25)	3 (75)	4
Total cases	89 (28)	224 (72)	313

which was more frequently associated single stone). Among the other changes, multiple stones were more associated with follicular cholecystitis, xanthogranulomatous cholecystitis, metaplasia (both gastric and intestinal), and carcinoma [Table 6].

While considering the type of stone, it was found that cholesterolosis was more common in patients with cholesterol stone; which is a well-known fact by now. Eosinophilic cholecystitis, follicular cholecystitis, and adenomatoid hyperplasia was associated with mixed stones only. Papillary hyperplasia did not show any significant predilection with any type of stone. Gastric metaplasia was a more common finding with mixed type (67.7%) of stone, whereas 80% of cases with intestinal metaplasia had combined stones. Three out of four cases of carcinoma had multiple mixed stones, while the remaining one had single combined stone.

DISCUSSION

In Northern India, gallstones are seven times more common with overall incidence of about 2.29%. A retrospective study of 346 patients was carried out to find out correlation between gallstones and GB mucosal changes. It is a well-known fact that a relationship exist between cholecystolithiasis and GB cancer as cholecystolithiasis is associated in over 80% of all GB cancer cases.[4] In one study, incidence of GB cancer is about 1.68%, whereas it is 3.5% in another study in which multiple histopathological section of GB was examined.[5] Coexistence of cholecystolithiasis with xanthogranulomatous cholecystitis, adenomyomatosis, and pyloric and intestinal metaplasia is well-known in literature. In our study, the age of patients ranged from 12 to 89 years. Majority of patients were in between 30 and 39 years. Main suffers were females with male: Female ratio being 1:4.2 an incidence similar to other studies.[6,7] Cholelithiasis is common in elderly females due to female sex hormone and sedentary habits.[8]

Table 6: Correlation of mucosal changes with morphology of stones

Type of lesion	Type of stone				
	Cholesterol (%)	Mixed (%)	Combined (%)	Pigment (%)	Total
Chronic cholecystitis	8 (4.5)	124 (68.5)	36 (19.8)	13 (7.2)	181
Acute on chronic cholecystitis	1 (3.3)	21 (70)	7 (23.4)	1 (3.3)	30
Cholesterolosis	5 (45.5)	1 (9.1)	4 (36.3)	1 (9.1)	11
Eosinophiliccholecystitis	0 (0)	1 (100)	0 (0)	0 (0)	1
Follicular cholecystitis	0 (0)	5 (100)	0 (0)	0 (0)	5
Xanthogranulomatouscholecystitis	0 (0)	7 (87.5)	1 (12.5)	0 (0)	8
Gangrenous cholecystitis	0 (0)	0 (0)	1 (100)	0 (0)	1
Papillary hyperplasia	1 (14.4)	3 (42.8)	3 (42.8)	0 (0)	7
Adenomatoid hyperplasia	0 (0)	4 (100)	0 (0)	0 (0)	4
Gastric metaplasia	1 (3.2)	21 (67.7)	7 (22.6)	2 (6.5)	31
Intestinal metaplasia	1 (3.3)	4 (13.4)	24 (80)	1 (3.3)	30
Carcinoma	0 (0)	3 (75)	1 (25)	0 (0)	4
Total cases	17 (5.4)	194 (62)	84 (26.8)	18 (5.8)	313

Mixed stones (70.55%) are most commonly encountered variety of gallstones in North India as in our study.[6,9] The incidence of cholesterol stones was in 5.43% (17/313), of pigmented stones was 5.75%, (18/313), of combined type was 20.76% (65/313), and of mixed type 68.05% (213/3130).

Single stones were in 95/313 (30.35%) and multiple stones were in 218/313 (69.64%) patients as in other reports.[7,10,11] This indicates that cases having multiple stones are more symptomatic (cholecystitis) than with single stone and mucosal changes like hyperplasia, metaplasia, and carcinoma were also more common in cases with multiple mixed type of stone.

In our study, when multiple section of GB like fundus, body, and neck, was scrutinized properly then dysplasia and carcinoma *in situ* were detected in 72/313 (23.00%) and 4/313 (1.27%) patients, respectively. In the study of Jukemura *et al*.,[5] reported 1.68% incidence of GB cancer in 475 removed GB when whole of the GBs were examined in totality. Precancerous GB mucosal changes have got clinical as well as pathological significance. However, theses changes are frequently overlooked by pathologist.[12]

In our study, GB mucosal hyperplasiawas found in 72/313 (23%) cases which is low as compared with Khanna *et al*., study where the incidence was 59%. Suffers were only females. The primary cholelithiasis causes mechanical mucosal irritation and result in hyperplasia.

Intestinal metaplasia was encountered in only 61/313 cases (19.480%). This incidence is comparable to other studies.[7] Only elderly females were suffer as in others reports.

Out of 313 cases of cholelithiasis, GB carcinoma was encountered in 1.27% (4/313). All affected patients were females and were in advance age group which is comparable with other reports.[13-16] The increased risk of GB cancer in women is partially explained by the higher incidence of cholecystolithiasis in women as compared with men. Female hormones may play a role in the etiology of this disease. Higher and extended exposure to female sex hormones may be a main factor. Therefore, early menarche, early first pregnancy, multiple pregnancies, and delayed menopause may increase the risk of GB carcinoma.[4]

GB metaplasia changes were common in patients with multiple mixed stone as in other studies. This association seem to be relative and statistical association could not be demonstrated between number stones and mucosal response.[8] Domeyer *et al*.,[12] reported that the solitary gall stones were important predictors of severe inflammation. Khanna *et al*.,[7] and Roa *et al*.,[17] could not document any association between the two in their respective studies.[15,17]

Xanthogranulomatous cholecystitis is an uncommon inflammatory and destructive GB process that can spread to adjacent structures and be confused with cancer. This histological alteration occurs in approximately 2% of all cholecystectomies, affects men and women equally and is frequently associated with gallstones. The occurrence of cancer in GBs with xanthogranulomatous cholecystitis has been reported and has been observed in 9-12% of these cases. Similarly, xanthogranulomatous cholecystitis presented a higher incidence within elderly individuals in this study and, interestingly, occurred more often among women.

In our study, the incidence of acute cholecystitis is higher in males as established in other studies. Acute cholecystitis has also been associated with cancer; however, in this study, there was no association between metaplastic lesions, dysplasia, or cancer and acute cholecystitis.[2]

With the advancing age the occurrence of cholecystolithiasis and GB cancer increases. An estimated 1% of the patients over the age of 65 with cholecystolithiasis may develop GB carcinoma, and it is related to the duration of gallstone disease rather than age of patients.[18] In our study, there were 4/313 cases of, adenomatoid hyperplasia which is

a non inflammatory benign GB alteration which mostly occurs in middle age patients, and its incidence increases with age. It is presently identified as a precancerous lesion, and cancer cases associated with areas of adenomyomatosis have been reported.[19]

In our study, incidence of metaplasia and dysplasia increased with the age and the metaplastic alterations and dysplasia are taken as precancerous lesions. Yamagiwa and Tomiyama analyzed 1,000 resected GBs and observed that the number of cases of dysplasia and cancer increased with age and the highest incidence was among patients with higher age group. The incidence of intestinal and gastric metaplasia was also higher in advance age group (as in our study).[13,15,17,20]

As GB cancer is extremely slow progressive disease, a prolong follow-up may be needed.[14] Ransohoff and Gracie[21] performed follow-up on 123 patients with asymptomatic cholecystolithiasis for seven years without incidence of GB cancer. Maringhini and associates performed follow-up on 2,583 patients for 13 years. During this period, five patients (0.2%) developed cancer.

Whether prophylactic cholecystectomy should be done in asymptomatic gallstones is still controversial. However, an Indian study recommends prophylactic cholecystectomies for asymptomatic gallstones in young patients with thickened GB wall (greater than 3 mm); with large gallstones (greater than 3 cm); patients with porcelain GB, sessile polyps (greater than 1 cm) and in peoples of areas with high incidence rates of GB cancer.[22]

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

CONCLUSION

The results of this study recommend that there may be a relationship between some histological changes of GB and cancer, and they also put forward that the metaplasia-dysplasia-carcinoma sequence could in fact be true in the case of GB carcinoma. Nevertheless, further studies are needed to understand GB carcinogenesis and risk factors.

REFERENCES

1. Albores-Saavedra J, Nadji M, Henson DE, Ziegels-Weissman J, Mones JM. Intestinal metaplasia of the gallbladder: A morphologic and immunocytochemical study. Hum Pathol 1986;17:614-20.
2. Lam CM, Yuen AW, Wai AC, Leung RM, Lee AY, Ng KK, *et al*. Gallbladder cancer presenting with acute cholecystitis: A population-based study. Surg Endosc 2005;19:697-701.
3. Shih SP, Schulick RD, Cameron JL, Lillemoe KD, Pitt HA, Choti MA, *et al*. Gallbladder cancer: The role of laparoscopy and radical resection. Ann Surg 2007;245:893-901.
4. Costa AL, Bresciani CJ, Perez RO, Bresciani BH, Sigueria SA, Cecconello I. Are histological alterations observed in the gallbladder precancerous lesions? Clinics (Sao Paulo) 2010;65:143-50.
5. Jukemura J, Leite KR, Machado MC, Montagnini AL, Penteado S, Abdo EE, *et al*. Frequency of incidental gallbladder carcinoma in Brazil. ABCD Arq Bras Cir Dig 1997;12:10-3.
6. Mohan H, Punia RP, Dhawan SB, Sekhon MS. Morphological spectrum of gallstone disease in 1100 cholecystectomies in north India. Indian J Surg 2005;67:140-2.
7. Khanna R, Chansuria R, Kumar M, Shukla HS. Histological changes in gallbladder due to stone disease. Indian J Surg 2006;68:201-4.
8. Mathur SK, Duhan A, Singh S, Aggarwal M, Aggarwal G, Sen R, *et al*. Correlation of gallstone characteristics with mucosal changes in gall bladder. Trop Gastroenterol 2012;33:39-44.
9. Tyagi SP, Tyagi N, Maheshwari V, Ashraf SM, Sahoo P. Morphological changes in diseased gall bladder: A study of 415 cholecystectomies at Aligarh. J Indian Med Assoc 1992;90:178-81.
10. Domeyer PJ, Sergentanis TN, Zagouri F, Tzilalts B, Mouzakioti E, Parasi A, *et al*. Chronic cholecystitis in elderly patients. Correlation of the severity of inflammation with the number and size of the stones. *In Vivo* 2008;22:269-72.
11. Juvonen T, Niemela O, Makela J, Kairaluoma MI. Characteristics of symptomatic gall bladder disease in patients with either solitary or multiple cholesterol gallstones. Hepatogastroenterology 1994;41:263-6.
12. Mukuda T, Andoh N, Matsushiro T. Precancerous lesions of the gallbladder mucosa. Tohoku J Exp Med 1985;145:387-94.
13. Yamagiwa H, Tomiyama H. Intestinal metaplasia-dysplasia-carcinoma sequence of the gallbladder. Acta Pathol Jpn 1986;36:989-97.
14. Maringhini A, Moreau JA, Melton LJ 3rd, Hench VS, Zinsmeister AR, DiMagno EP. Gallstones, gallbladder cancer and other gastrointestinal malignancies. An epidemiologic study in Rochester, Minnesota. Ann Intern Med 1987;107:30-5.
15. Tazuma S, Kajiyama G. Carcinogenesis of malignant lesions of the gallbladder. The impact of chronic inflammation and gallstones. Lagenbecks Arch Surg 2001;386:224-9.
16. Kayahara M, Nagakawa T. Recent trends of gallbladder cancer in Japan: An analisis of 4770 patients. Cancer 2007;110:572-80.
17. Roa I, de Aretxabala X, Araya JC, Roa J. Preneoplastic lesions in gallbladder cancer. J Surg Oncol 2006;93:615-23.
18. Sheth S, Bedford A, Chopra S. Primary gallbladder cancer: Recognition of risk factors and the role of prophylactic cholecystectomy. Am J Gastroenterol 2000;95:1402-10.
19. Aldridge MC, Gruffaz F, Castaing D, Bismuth H. Adenomyomatosis of the gallbladder. A premalignant lesion? Surgery 1991;109:107-10.
20. Duarte I, Llanos O, Domke H, Harz C, Valdivieso V. Metaplasia and precursor lesions of gallbladder carcinoma. Frequency, distribution, and probability of detection in routine histologic samples. Cancer 1993;72:1878-84.
21. Gracie WA, Ransohoff DF. The natural history of silent gallstones: The innocent gallstone is not a myth. N Engl J Med 1982;307:798-800.
22. Kapoor VK. Cholecystectomy in patients with asymptomatic gallstone to prevent gallbladder cancer–the case against. Indian J Gastroenterol 2006;25:152-4.

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