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Original Research Article

Histopathological spectrum of gallstone disease from cholecystectomy specimen in rural areas of West Bengal, India- an approach of association between gallstone disease and gallbladder carcinoma

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ABSTRACT

Background: Gallstone disease (GSD) is a common health problem throughout the world and majority of this burden occurs in developing countries. Most of the gallbladder carcinoma (GBC) is associated with GSD but there is till deficit of information on this association. Beside this, there is no study on the spectrum of histopathological pattern of cholecystectomy specimens from GSD patients in rural areas of West Bengal of India.
Methods: The study was carried out on GSD patients who were undergone for cholecystectomy at B.S. Medical College & Hospital of West Bengal over a period of three years from January 2013 to December 2015. Histopathological reports of cholecystectomy specimens were analyzed.
Results: In the present study, total 786 GSD patients were included where 635 were female and 151 were male. Histopathological findings depicted that chronic cholecystitis was the most prevalent (79.8%) followed by acute-on-chronic cholecystitis (6.1%), cholesterolosis (2.9%) and xanthogranulomatous cholecystitis (1.7%) among the patients. Beside these, hyperplasia, metaplasia, dysplasia and GBC were observed in 2.0%, 4.7%, 2.2% and 0.6% of the patients respectively. The mean ages for patients with chronic cholecystitis, hyperplasia, metaplasia, dysplasia and carcinoma were 34.5, 37.2, 42.9, 43.9 and 53 years respectively. Study also showed that male GSD patients were more prone to pre-malignancy and malignancy (significant at 95% confidence limit).
Conclusions: The study revealed that different types of histopathological features were present in the gallbladder of GSD patients where pre-malignant (hyperplasia, metaplasia and dysplasia) and malignant types were remarkable percentages though chronic cholecystitis was the commonest histopathological feature. Study also demonstrated that males with GSD were more prone to pre-malignancy and malignancy. Gradient ages may suggest that GBC was developed from cholecystitis to carcinoma via hyperplasia, metaplasia and dysplasia.

Keywords: Cholecystectomy, Gallstone diseases, Histopathology, Malignancy, Pre-malignancy

INTRODUCTION

Gallstone disease (GSD) is one of the major gastrointestinal disorders, which is formed mainly due to metabolic problems of hepato-biliary system.[1,2] It is a common health problem worldwide but its prevalence varies country to country where it is found 2-29% in India.[3-6] Prevalence of GSD also varies with age, sex, and

ethnic group.[7] GSD itself is not only gastrointestinal metabolic disorder presenting pain in the right upper quadrant with digestive complain but also it helps to develop the pathology in gallbladder cells or tissues where gallbladder carcinoma (GBC) is most fatal transformation.[6,8,9] Hyperplasia and metaplasia of the gallbladder are the precursors of dysplasia and dysplasia itself is a potential condition of carcinoma.[10-12] Therefore all these pre-malignant conditions in gallbladder may also boost the chances of GBC.

GBC is one of the worst of cancer mortality and, which is 5th most common gastrointestinal malignancy in India following colon, pancreas, stomach and esophagus.[13] Obesity, reproductive factors, genetic factors, life style risk factors (cigarette smoking, alcohol consumption etc.), chronic infections of the gallbladder, environmental exposure to specific chemicals, gallstones and so many factors are responsible for the development of GBC but gallstones are said to have major role in causation of GBC.[9,14-16] It has been reported that large size of gallstone and longstanding of chronic GSD are acts as high risk factors for the development of GBC, which has been accounted to have increased four to seven times.[9,16,17]

In India, the prevalence of GBC varies on geographical distribution whereas it is higher in North India compared to South India.[17] The incidence of GBC varies from 0.3 to 12 % of GSD patients in India and other countries, where about 0.5-1.1% of all elective cholecystectomies performed for cholelithiasis harbor an occult GBC.[18-22] On another hand, gallstones are found in 74-92% of GBC patients in India.[23,24]

Most of the patients are unaware about the GSD and remain asymptomatic for a long period. Only small percentages develop symptoms necessitating treatment at early stage.[25] It is found that generally this untreated chronic GSD may cause chronic inflammation of gallbladder and likely to promote carcinogenesis, though the definite etiology of GBC has been a source of speculation.[26] However, GSD and its after effect in gallbladder tissues is very important issue to prevent the GBC in the community, especially in the population of rural and backward area where untreated chronic GSD is very common. Beside this, the exact magnitude of the histopathological spectrum from cholecystectomy specimens of GSD patients in rural India is still obscure. The knowledge of prevalence and distribution of the gallbladder abnormalities developed due to GSD aiding in prevention of GBC plays a vital role in management of GSD patients as well as in the formulation of prevention policies of GBC. Beside this, study of association between GSD and GBC is very important for better understanding of the disease. Therefore, the study aimed for providing the information on the spectrum of histopathology from the cholecystectomy specimens of GSD patients in the rural population of West Bengal who visited Bankura Sammilani Medical College & Hospital (BSMC&H), Bankura, West Bengal, India.

METHODS

Selection of subject

In the three consecutive years from January 2013 to December 2015, the patents those who were underwent for cholecystectomy due to GSD in the Surgical Department of BSMC & H, were included in this study. Name, age, sex and clinical details were recorded for this study. BSMC & H is a rural based Government Medical College Hospital.

Histopathological examinations

The cholecystectomy specimens from the Surgery Department were sent for histopathological examination in the Pathology Department of this institute. For the proceeding of histopathological examination, sections were taken from the fundus, body and neck of the gall bladder and additional sections were taken from abnormal appearing mucosa. Then, the samples were processed for routine hematoxylin and eosin staining for microscopic examination. All the examinations regarding histopathology diagnosis were performed by the expert faculties of the department.

Pre-malignant (PM) and malignant (M) cases were denoted together as 'PM-M conditions' where hyperplasia, metaplasia and dysplasia were the pre-malignant conditions. Data of average age presents as Mean±SD. Statistical analysis was run in a table by using Z test.

RESULTS

A total of 786 GSD patients were undergone for cholecystectomy during the above mentioned three years. Among these patients, majority (80.8%) were female and only 19.2% were male. The age of the patients ranged from 13 to 76 years. Results showed that in case of female, majority of GSD patients represented from lower age group and it was decline pattern with increase of age but it showed opposite manner in case of male participants (Figure 1).

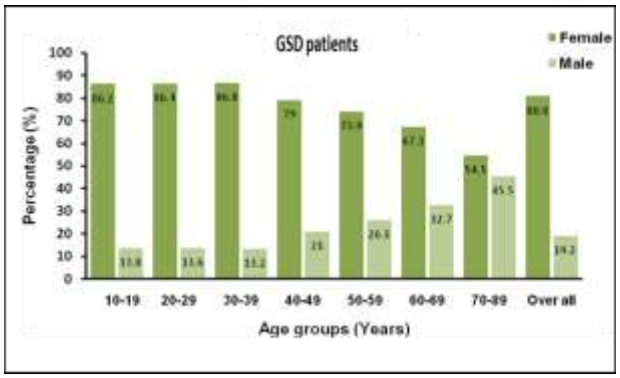

Figure 1: Age group and sex wise distribution of GSD patients (n=786).

Details of the histopathological findings with number of cases are shown in Table 1. Histopathological observations from cholecystectomy specimens showed that chronic cholecystitis, acute-on-chronic cholecystitis, cholesterolosis, xanthogranulomatous cholecystitis (XGC), hyperplasia, metaplasia, dysplasia and carcinoma were found in 627 (79.8%), 48 (6.1%), 23 (2.9%), 13 (1.7%), 16 (2.0%), 37 (4.7%), 17 (2.2%) and 5 (0.6%) cases respectively. Among the hyperplasia, 4 cases were adenomatous hyperplasia, 10 cases were glandular hyperplasia and 2 cases were reactive hyperplasia where pyloric metaplasia and intestinal metaplasia were found in 19 and 18 cases respectively among the metaplasia. PM-M conditions (hyperplasia, metaplasia, dysplasia and carcinoma cases) were found in total 75 (9.5%) patients among the GSD patients.

Table 1: Distribution of histopathological varieties of cholecystectomy specimens of GSD patients.

Types of histopathology		No. of cases		
Types	**Varieties**	**Female**	**Male**	**Total**
Chronic cholecystitis		524 (83.6)	103 (16.4)	627
Acute-on-chronic cholecystitis		32 (66.7)	16 (33.3)	48
Cholesterolosis		18 (78.3)	05 (21.7)	23
Xanthogranulomatous cholecystitis		08 (61.5)	05 (38.5)	13
Hyperplasia	Adenomatous	03 (75.0)	01 (25.0)	04
	Glandular	07 (70.0)	03 (30.0)	10
	Reactive	01 (50.0)	01 (50.0)	02
Metaplasia	Pyloric	14 (73.7)	05 (26.3)	19
	Intestinal	13 (72.2)	05 (27.8)	18
Dysplasia		11 (64.7)	06 (35.3)	17
Carcinoma	**Adenocarcinoma**	03 (60.0)	02 (40.0)	05
	Total	635 (80.8)	151 (19.2)	786

Age group wise analysis showed that highest number of non-malignant cases (25.6%) was found in 20-29 years of age groups but highest numbers of pre-malignant and malignant cases (33.3%) were detected in 40-49 years of age groups. The maximum frequency of chronic cholecystitis, hyperplasia, metaplasia, dysplasia and carcinoma conditions were observed in 20-29 years, 20-29 years, 40-49 years, 40-49 years and 40-59 years of age group respectively (Table 2-4). Consequently, the average age of patients of chronic cholecystitis, hyperplasia, metaplasia, dysplasia and carcinoma conditions were noticed in 34.5±14.3, 37.2±10.2, 42.9±13.0, 43.9±11.3 and 53.0±8.4 years respectively (Table 4).

Out of 75 PM-M cases, 53 cases (among 635 female) were female and 22 cases were male (among 151 male). Therefore, the proportion of male (14.6%) was seen greater than female (8.4%) which was statistically significant ($p<0.05$) (Table 5).

Table 2: Age wise distribution of gallbladder histopathological spectrum of GSD patients (n=786) with special reference to non-malignant types.

Age groups (years)	CC (%)	Acute-on- CC (%)	Cholesterolosis (%)	XGC (%)	Over all (%)
10-19	27 (4.3)	2 (4.2)	0	0	29 (4.1)
20-29	164 (26.1)	12 (25.0)	3 (13.0)	3 (23.1)	182 (25.6)
30-39	149 (23.8)	9 (18.7)	5 (21.7)	1 (7.7)	164 (23.1)
40-49	130 (20.7)	14 (29.2)	9 (39.1)	3 (23.1)	156 (21.9)
50-59	107 (17.1)	8 (16.7)	5 (21.7)	4 (30.7)	124 (17.4)
60-69	40 (6.4)	3 (6.2)	1 (4.3)	2 (15.4)	46 (6.5)
70-79	10 (1.6)	0	0	0	10 (1.4)
Total [%]	**627 (100)** [79.8]	**48 (100)** [6.1]	**23 (100)** [2.9]	**1 3(100** [1.7]	**711 (100)** [90.5]

Figure in third bracket parenthesis in row wise indicates the percentage out of total number study subjects. XGC - Xanthogranulomatous cholecystitis, CC - Chronic Cholecystitis.

Table 3: Age wise distribution of gallbladder histopathological spectrum of GSD patients (n=786) with special reference to pre-malignant (hyperplasia, metaplasia and dysplasia) and malignant types

Age groups (years)	Hyperplasia (%)	Metaplasia (%)	Dysplasia (%)	Carcinoma (%)	Over all (%)
20-29	6 (37.5)	9 (24.3)	1 (5.9)	0	16 (21.3)
30-39	3 (18.8)	2 (5.4)	5 (29.4)	0	10 (13.3)
40-49	3 (18.8)	14 (37.8)	6 (35.3)	2 (40.0)	25 (33.3)
50-59	3 (18.8)	7 (18.9)	2 (11.8)	2 (40.0)	14 (18.7)
60-69	1 (6.2)	4 (10.8)	3 (17.6)	1 (20.0)	9 (12.0)
70-79	0	1 (2.7)	0	0	1 (1.3)
Total [%]	**16 (100)** [2.0]	**37 (100)** [4.7]	**17 (100)** [2.2]	**5 (100)** [0.6]	**75 (100)** [9.5]

Figure in third bracket parenthesis in row wise indicates the percentage out of total number study subjects.

Table 4: Number and age distribution of GSD patients with various histopathological features (n=786).

Epithelial changes	No. of patients (%)	Mean age±SD (Range)	Age group of highest patients frequency (Mean age±SD)	No of patients in the age group (%)
Chronic cholecystitis	627 (79.8)	34.5±14.3 (14-72)	20-29 (23.8±2.7)	164 (26.1)
Hyperplasia	16 (2.0)	37.2±10.2 (26-55)	20-29 (28.1±1.3)	6 (37.7)
Metaplasia	37 (4.7)	42.9±13.0 (25-78)	40-49 (43.9±2.8)	14 (37.8)
Dysplasia	17 (2.2)	43.9±11.3 (26-65)	40-49 (43.9±2.8)	6 (35.3)
Carcinoma	5 (0.6)	53.0±8.4 (45-65)	40-59 (50.2±5.8)	4 (80.0)

Age represents in years; Frequency means no. of patients.

Table 5: Incidence of gallbladder pre-malignant and malignant (GB PM-M) condition among GSD patients between male and female.

Patient types	Male	Female	Statistical value
GSD	151	635	Z =2.02*
GB PM-M condition among GSD	22 (14.6%)	53 (8.4%)	

*A statistical significant difference was found between male and female (Z is greater than 1.96 (the critical level of significance), hence significant at 95% confidence limits).

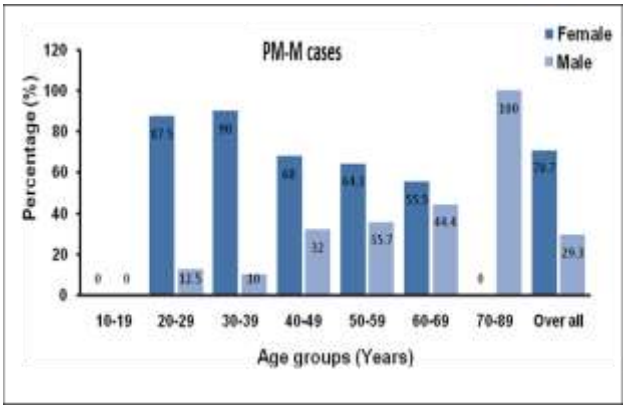

Figure 2: Age group and sex wise distribution of PM-M cases (n=75).

PM-M condition was not found bellow 20 years of age but the GSD was noticed in all age groups. Male cases of PM-M conditions presented comparatively higher number with gradual increase in higher age groups than lower age groups where female showed a reverse condition though female were more prevalent in each age groups except the oldest age group (70-79 years) (Figure 2). Comparatively higher percentages of male cases in PM-M conditions in respect to male GSD patients were found in higher age groups (Figure 1 and Figure 2).

DISCUSSION

GSD is worldwide occurrence, though some geographical areas have high prevalence of this disorder.[3-6] The abnormal pathological development in gallbladder tissue

due to GSD is a common problem but development of its different types remains precarious.[6] Specially, development of malignant type is one of the important concerns of public health problems as less than 5% of its malignant cases with advanced stages can survive for 5 years.[27]

In the present study, chronic cholecystitis was the most common histopathological findings which was observed in 79.9 % cases and followed by 6.1% cases of acute-on-chronic cholecystitis, 2.9% cases of cholesterolosis and 1.7 % cases of XGC. Beside these, 2.0% cases as hyperplasia (adenomatous, glandular and reactive type), 4.7% cases as metaplasia (pyloric and intestinal type), 2.2% cases as dysplasia and 0.6% cases as adenocarcinoma of gallbladder encountered in this study. A study conducted at Rohtak, State of Hariana, India, it was observed that chronic cholecystitis in 45%, acute-on-chronic cholecystitis in 12%, follicular cholecystitis in 5%, XGC in 3%, cholesterolosis in 6% and hyperplasia in 8% (adenomatous in 6% and adenomyomatous in 2%), metaplasia in 18% (intestinal type in 8% and pyloric type in 10%) and carcinoma in 2% of the patients were detected among the 330 cholecystectomy specimens of GSD patients.[29] A recent study by Siddiqui et al found that 92.3% as chronic cholecystitis cases, 4.5% as acute-on-chronic cholecystitis cases and 2.7% as adenocarcinoma cases among 220 patients with gallstones in Pakistan.[28]

Among the GSD patients of this study, total 8.9% of the patients encountered as premalignant condition and 0.6% as malignant condition, and overall 9.5% cases were observed as PM-M conditions, means this 9.5% of the patients is involved in the transformation of pre-malignancy or malignancy of gallbladder which may be caused due to GSD. These pre-malignant cases may be transformed into malignancy due to long period exposure of gallstone in the gallbladder that may come from delay of treatment.[14,15] Percentage of these transformations is very remarkable and its population proportion is expected to be within 7.4% and 11.6% (95% confidence limit) among GSD patients in the study area.

The present study indicates that female was more suffered with GSD compare with male and it was persist in each age group but percentages of females were decreased with increase of ages and conversely males were gradually increased with increase of ages. Most probably male showed late age presentation of the disease and therefore they were increased in later age groups for seeking the treatment (cholecystectomy) and this late age presentation may be responsible for increasing the chances of PM-M conditions in male. Already our result shows that proportion of male GSD patients are statistically significant high in the development of PM-M conditions. On other hand, females may be presented the symptoms of the disease at early ages and therefore they were comparatively higher in number for seeking treatment at early ages than the later ages. This early age presentation may be reason for decreasing the chances of PM-M conditions in female. In higher age groups, comparatively higher percentages of male cases of PM-M conditions in respect to the percentages of male GSD patients may also support the phenomenon of late age presentation in male. It is cleared that female were more prevailed to PM-M conditions as major percentages of GSD were in female but male GSD patients were high chances to the development of PM-M conditions. Most of the studies show that GBC is more dominant in female.[9,17,20,29,30] A study by Alvi et al also observed that male was comparatively dominant in gallbladder cancer group of gallstone patients.[31] Several studies suggest that majority of the patients remain asymptomatic for a long period and they are unaware about the GSD.[7,14,15,25] It is found that generally this untreated chronic GSD may cause chronic inflammation of gallbladder and likely to promote carcinogenesis.[26]

The study focused that highest frequency of non-malignant cases were encountered in 20-29 years of age groups but highest frequency of PM-M conditions were observed in 40-49 years of age groups where hyperplasia, metaplasia, dysplasia and carcinoma conditions were found in 20-29 years, 40-49 years, 40-49 years and 40-59 years of age groups respectively and the mean ages of patients of chronic cholecystitis, hyperplasia, metaplasia, dysplasia and carcinoma conditions were noticed in 34.5±14.3, 37.2±10.2, 42.9±13.0, 43.9±11.3 and 53.0±8.4 years respectively. So it indicates that increase of age of the patients is related with the severity of gallbladder transformation towards malignancy and these degrees of transformation may depend on period of gallstone exposure. Similarly, a study by Alvi et al also showed that patients with long period of exposure of gallstone were independent risk factors for development of GBC.[31] Several studies showed that GBC was found in aged patients of GSD.[31,32] Mukhopadhyaya and Landas also observed that increase of age of the patients was related to transformation of gallbladder epithelium from metaplasia to dysplasia where mean ages for patients with antral-type metaplasia, intestinal metaplasia and dysplasia were 49.4, 50.9 and 52.6 years respectively.[10] Scientist Wistuba and Gazdar predicted in a very recent hypothesis of 'model of multi-step pathogenesis of gallbladder cancer from gallstones' that the longstanding gallstone may change the normal gallbladder mucosa leading to malignancy following the progress of chronic cholecystitis to hyperplasia to metaplasia to dysplasia and to carcinoma.[27] Few studies have reported that around 10-15 years is required to transform from dysplasia to neoplasia in gallbladder.[33,34]

CONCLUSION

The study revealed that chronic cholecystitis was the commonest histopathological feature but pre-malignant and malignant cases were present in remarkable number in the rural areas of West Bengal, India. Female were more prevailed to PM-M conditions as major percentages

of GSD were in female but male GSD patients were more prone to the development of pre-malignancy and malignancy. Age gradient of patients from chronic cholecystitis to carcinoma strengthen the hypothesis of progression from chronic cholecystitis to carcinoma via hyperplasia to metaplasia to dysplasia. Above all, all these observations may suggest an association between GSD and development of GBC. The factors in the gallstones, which mainly play for transformations of gallbladder into pre-malignancy or malignancy, are to be investigated.

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