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Original Research Article

Premalignant Epithelial Lesions of Gall Bladder: A Histopathological Study

Gajender Singh[1], Satyaveer Kumar Mathur[2], Padam Parmar[3], Sant Prakash Kataria[4], Sunita Singh[3], Sucheta Malik[5], Yashika Bhatia[5]

[1]Associate Professor, [2]Senior Professor, [3]Senior Resident, [4]Professor, [5]Resident,
Department of Pathology, PT BDS PGIMS, Rohtak, Haryana.

Corresponding Author: Padam Parmar

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ABSTRACT

Objective: Association of primary gall bladder cancer with other epithelial changes has been observed during the last decades. Most commonly, cholelithiasis produces a series of epithelial pathological changes which could be precursor lesions of gallbladder cancer in background of inflammation. These changes include hyperplasia, dysplasia and metaplasia. We conducted the study to evaluate the incidence of these precursor epithelial changes in the gall bladder of patient undergoing cholecystectomy.

Materials and methods: A total of 100 consecutive specimens of gall bladder were taken up for present study. Specimen was fixed and processed by routine histological technique for paraffin embedding. Six cross sections of each gall bladder (2 each from fundus, body and neck) were extensively studied. Conventional Haematoxylin and eosin (H & E) stained microsections prepared from the specimens and evaluated for various histological epithelial changes.

Results: The maximum number of patients in which cholecystectomy was performed were between 31 to 50 years age group (62%). Out of 100 cases, 83 were females (83%) and 17 were males (17%). Among total cases, 98 turned out to be benign and 2 were malignant. Out of the 98 benign lesions, the most common histopathological diagnosis established was of chronic cholecystitis in 90 cases forming 91.84% of the total benign lesions. Hyperplasia was found in 49 (52.69%), metaplasia in 34 (36.56%) and dysplasia in 10 (10.75%) cases. Out of 49 cases of hyperplasia, simple hyperplasia was found in 20 cases followed by papillary in 18 cases. Intestinal type metaplasia (n=24) was predominant over pyloric (n=10). Only two cases of carcinoma were encountered, both of which were adenocarcinoma, histologically.

Conclusion: Various epithelial pathological changes in the gallbladder mucosa must be rule out with extensive histological examination to prevent future development of carcinoma.

Keywords: Gall bladder, premalignant lesions, cholecystitis, hyperplasia, metaplasia.

INTRODUCTION

Precancerous changes of gall bladder epithelium are of considerable importance due to progression of these lesions into malignancy. Improved diagnostic procedures including radiological and histopathological examinations may reveal early or resectable invasive carcinoma more frequently. Surgically removed gall bladders from patients without overt signs of carcinoma may reveal the presence of a variety of epithelial abnormalities including dysplasia and carcinoma in situ. [1]

Long standing inflammation irrespective of underlying causes is important in the development of abnormal epithelial lesions and possibly in future development of cancer. Frequently, chronic

cholecystitis presents a large range of associated lesions like cholesterolosis, muscle hypertrophy, parietal fibrosis, polypoid and adenomatous proliferation of mucous glands, metaplasia and dysplasia of epithelium. [2,3]

Incidence of carcinoma of the gallbladder in India is 2.3 and 1.01 per 100,000 in female and male population respectively. In 70-98% cases of gallbladder cancer, gall stones are important risk factor among the various risk factors. [4,5] Incidence of cholelithiasis is higher in older age group and in females. Female sex hormones and sedentary habits expose them to factors that possibly promote formation of gallstones. [3] A significantly higher incidence of carcinoma gall bladder has been observed in patient with gallstones for longer duration which progress from various epithelial lesions. [2] Hyperplastic and atypical epithelial lesions of the gall bladder have been considered potential precursors of the invasive carcinoma. Prolonged irritation by gall stones or chronic inflammation leads to metaplastic changes of the gall bladder mucosa which may occasionally lead to development of carcinoma. [4,5] We evaluated the incidence of these epithelial changes in the gall bladder of patient undergoing cholecystectomy for various surgical indications.

MATERIALS AND METHODS

A total of 100 consequative specimens of gall bladder received in the Department of Pathology were taken up for present study. Specimen was fixed and processed by routine histological technique [6] for paraffin embedding. Six cross sections of each gall bladder (2 each from fundus, body and neck) were extensively studied to categorize the premalignant epithelial lesions of the gall bladder. Additional sections were taken from abnormal-appearing areas. Conventional Haematoxylin and eosin (H & E) stained microsections prepared from the specimens were examined and wherever necessary special stains such as alcian blue, periodic acid Schiff and reticulin stains were employed.

RESULTS

In this study, the youngest patient was 5 years old and the oldest was 80 years of age. The maximum number of patients in which cholecystectomy was performed were between 31 to 50 years age group i.e. 62 cases forming 62% of the study group. (Table 1) Out of 100 cases, 83 were females (83%) and 17 were males (17%). (Figure 1) Among total cases, 98 turned out to be benign and 2 were malignant (Figure 2).

Table 1: Age Distribution Of Patients

Age (in years)	Number of patients	Percentage (%)
0-10	1	1
11-20	3	3
21-30	13	13
31-40	36	36
41-50	26	26
51-60	11	11
61-70	8	8
71-80	2	2
Total	**100**	**100**

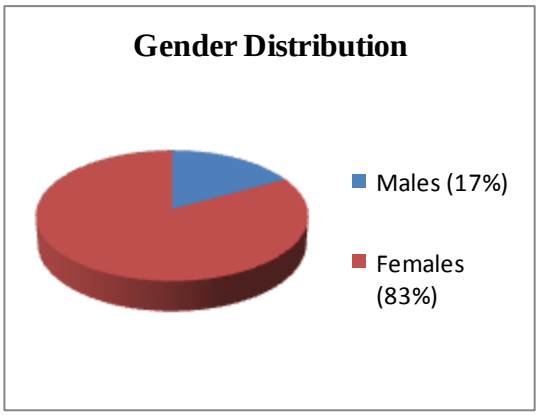

Figure 1

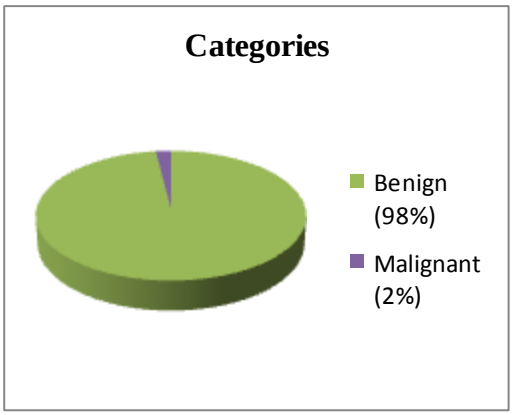

Figure 2

Out of the 98 benign lesions, the most common histopathological diagnosis established was of chronic cholecystitis (n=90), forming 91.84% of the total benign lesions. Acute or chronic cholecystitis was observed in 5 cases (5.10%), follicular cholecystitis in 1 case (1.02%), Xanthogranulomatous cholecystitis (XGC) in 2 cases (2.04) in benign category. (Table 2) Maximum numbers of benign cases (62.24%) were observed in age group of 31 to 50 years. Lesser number of cases i.e. 13 (13.27%) and 11 (11.23%) were found in the age group of 21-30 and 51-60 years respectively.

Hyperplasia was found in 49 (52.69%), metaplasia in 34 (36.56%) and dysplasia in 10 (10.75%) cases. All cases of hyperplasia and metaplasia had associated cholecystitis, as compared to dysplasia in which only 80% of cases had association with cholecystitis. This was in contrast to association with cholelithiasis which showed maximum association with metaplasia (91.1%). (Table 3) Out of 49 cases of hyperplasia, simple hyperplasia was found in 20 cases followed by papillary in 18 cases. Intestinal type metaplasia (n=24) was predominate over pyloric (n=10). (Table 4) Only two cases of carcinoma were encountered, both of which were adenocarcinoma, histologically.

Table 2: Distribution of Benign Lesions (N=98)

Diagnosis	Number of lesions	Percentage (%)
Chronic cholecystitis	90	91.84
Acute on chronic cholecystitis	05	5.10
Follicular cholecystitis	01	1.02
Xanthogranulomatous cholecystitis	02	2.04

Table 3: Association of Premalignant Lesions With Cholecystitis And Cholelithiasis

Premalignant lesions	Number of lesions	Cholecystitis		Cholelithiasis	
		Number	Percentage	Number	Percentage
Hyperplasia	49	49	100	37	75.5
Metaplasia	34	34	100	31	91.1
Dysplasia	10	08	80	05	50
Total	93	91	97.84	73	78.49

Table 4: Distribution of Premalignant Gall Bladder Lesions

Premalignant lesions		Number of lesions		Percentage %
Hyperplasia	Simple	49	20	21.50
	Papillary		18	19.36
	Adenomatous		9	9.67
	Tubule-villous		2	2.15
Metaplasia	Intestinal	34	24	25.81
	Pyloric		10	10.76
Dysplasia	Mild	10	8	8.60
	Moderate to severe		2	2.15
Total		93	93	100

DISCUSSION

Various risk factors have been associated with carcinoma gall bladder. Cholelithiasis produces diverse stone disease with various histopathological changes in mucosa including acute inflammation, chronic inflammation, granulomatous inflammation, hyperplasia and dysphasia. With improved diagnostic procedures including extensive histological examination of gall bladder mucosa may reveal the presence of a variety of epithelial abnormalities in early stage and prevent development of cancer from these lesions. [1]

In our study 36% cases were between 31 to 40 years of age followed by 26% between in 41-50 years. This is similar to the findings by Albores et al [7] in which 61% of patients were 40 years of age or older. In a study by Tyagi et al, [8] out of 415 cholecystectomy cases, 63.4% cases were in 4^{th} and 5^{th} decade. Ojeda et al [9] studied 120 cholecystectomy specimens and observed 39.16% cases were between 41 to 60 years of age group. Kozuka et al [10] studied 500 cholecystectomy cases ranged in age from 21 to 87 years with a peak incidence of patients in the fifth decade. Mohan H et al [4] studied 1100 gall bladder specimen with maximum number of cases (316, 28.7%)

between age group 31-40 years. Female predominance was found to be similar to various other studies. [4,5 ,7 ,9 ,10-12] (Table 5)

Table 5: Gender wise distribution in various studies

Study	No of cases	Males (%)	Females (%)
Albores et al [7]	100	11	89
Ojeda et al [9]	120	30	70
Duarte et al [11]	100	24	76
Kozuka et al [10]	110	39	61
Mukada et al [12]	100	37	63
Khanna R et al [5]	140	24	116
Mohan H et al [4]	1100	148	952
Our study	100	17	83

In our study, most common benign histopathological diagnosis was chronic cholecystitis (91.84%). Ojeda et al and Mukada et al [12] found chronic cholecystitis in 86% and 82% of the cases. However, Tyagi et al [8] found chronic cholecystitis in 50.8% cases only. They also observed acute or chronic cholecystitis in 10.8% xanthogranulomatous cholecystitis (XGC) in 4.1% and follicular cholecystitis in 6.2% cases. [10] In our study we had 5.10% cases of acute or chronic cholecystitis, follicular cholecystitis in 1.02% and XGC in 2.04% cases. Study by Mohan H et al, [4] chronic cholecystitis was present in 100% of cases. XGC and follicular cholecystitis was present at same frequency (2.3%) in their study.

Cholelithiasis was observed in 73% cases in our study. This is comparable with the study by Albores et al, [7] in which cholelithiasis was found in 79.5% cases. Tyagi et al [8] and Ojeda et al [9] observed gall stones in 85.3% and 83% cases. However, Mukada et al [12] found cholelithiasis in 87.4% of cases. Duarte et al [11] in their study on 162 cholecystectomy specimens had cholelithiasis in 100% cases. Mohan H et al [4] observed gall stone in 95.4% specimen.

In our study, premalignant epithelial lesions were observed in 93 cases (93%) out of total 100 cases. Hyperplasia was seen in 49 cases (49%), metaplasia in 34 cases (34%) and dysplasia in 10 cases (10%). All cases of hyperplasia were associated with chronic cholecystitis. However, hyperplasia was associated with cholelithiasis in 75.5% cases. This is comparable to study by Mukada et al [12] in which they reported hyperplasia in 27% of cases, chronic cholecystitis in 90.7% and cholelithiasis in 90.4% cases. Duarte et al [11] reported incidence of hyperplasia in 46.9% of cases which is almost same as in our study. However, Albores et al [7] reported hyperplasia in 83% of cases, out of which 79.5% had cholecystitis.

In our study, there were 10 cases (10%) of dysplasia. Eighty percent cases of dysplasia had chronic cholecystitis and 50% cases had associated cholelithiasis. This is comparable with findings by Mukada et al [12] in which they found dysplasia in 14.5% of cases. Associated chronic cholecystitis and cholelithiasis was seen in 93.1% and 82.8% of cases respectively. This is also comparable to study by Tyagi et al [8] (9.5%) and Albores et al [7] (13.5%). However, Duarte et al [11] reported a higher incidence of dysplasia i.e. (16%). Ojeda et al [9] found lower incidence of dysplasia, i.e., 3.3%. [6] Normal epithelium was seen in 13 specimens (9%) in study by Khanna R et al [5] however they examined the specimen of gall bladder with stones only. Epithelial hyperplasia was observed in 83 (69%), antral metaplasia in 23 (16.5%), intestinal metaplasia in 22 (15.5%), dysplasia in 12 (8.5%) and carcinoma in situ in 1 specimen (0.7%). Fibrosis and ulceration was found in 26 specimens (19%).

Table 6: Frequency of Premalignant Lesions In Various Studies

Study	Cases having following premalignant epithelial lesions (%)	
	Hyperplasia	Dysplasia
Our study	49	10
Mukada et al [12]	27	14.5
Tyagi et al [8]	62.5	9.5
Albores et al [7]	83	13.5
Duarte et al [11]	46.9	16
Ojeda et al [9]	-	3.3
Khanna R et al [5]	69	8.5

There were 34 cases (34%) of metaplasia in our study. This is in conformity to the study by Azadeh et al [13] in which they found metaplasia (intestinal and pyloric) in 35% cases. However, other studies have found a higher incidence of

intestinal and pyloric metaplasia. Study by Laitio M [14] of 103 gall bladder found that 75 (72.8%) gall bladder contained at least one type of metaplasia such as goblet cells, enterochromaffin cells, gastric type cells or intestinal type mucosal cells.

Only 2 cases (2%) of carcinoma were diagnosed, both of which were adenocarcinoma histologically. Both the cases of carcinoma were females aged 35 years and 70 years. This finding is almost consistent with the study by Mukada et al [12] in which they found 1% cases of occult invasive carcinoma. This is also corresponding to the finding by Bhansali SK et al, [15] who reported carcinoma gall bladder in 2.5% cases. Mohan H et al [4] observed only 12 (1.09%) cases out 1100 case of carcinoma gall bladder. Khanna R et al [5] didn't observe any case of carcinoma out of 140 consecutive specimens.

CONCLUSION

Various epithelial pathological changes in the gallbladder mucosa must be rule out with clinic-radiological examination and extensive histological examination to prevent cancer related morbidity and mortality.

Conflict of interest: All authors state that there are no conflicts of interests.

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