

Precancerous Lesions in Routine Cholecystectomy Specimens

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ABSTRACT

Objective: To determine the frequency of precancerous lesions in routine cholecystectomy specimens.

Study Design: Observational, descriptive study.

Place & Duration: Department of Histopathology, Pakistan Naval Ship (PNS) Shifa Karachi, from January to December 2010.

Material and Methods: A total of 292 Cholecystectomy specimens were included in this study. After gross examination the representative sections were taken, processed and embedded in paraffin as per standard procedure, 4 μ thick paraffin sections were cut and stained with hematoxylin and eosin followed by microscopic examination. Documentation including the hospital identification number, laboratory number, date of receipt of the specimen, patient's age /sex duration of disease, pre operative diagnosis, microscopic description and diagnosis were noted down on a proforma. Data was analyzed on Statistical Package for Social Sciences (SPSS) version 16.0.

Results: Majority of the patients 33.22% (n=97) were recorded between 41-50 years of age, 27.05% (n=79) were found with 51-60 years, 23.29% (n=68) with 31-40 years while 16.44% (n=48) was found between 20-30 years of age. The mean age was recorded as 42.7 with 1.24 S.D. Among 292 cases 84.25% (n=246) were female and 15.75% (n=46) were male. The status of precancerous lesion(s) squamous metaplastic lesions were found in 13.01% (n=38), metaplastic intestinal in 8.92% (n=26), dysplastic in 7.53% (n=22) and other non-precancerous changes were found in 70.5% (n=206). Majority of the patients 51.16% (n=44) having history of 1-2 years duration of the disease, 23.25% (n=20) with 2-3 years while 25.59% (n=22) with >3 years. Chronic cholecystitis and cholelithiasis was found in all (100%) cases, with multiple small stones were found in 66.27% (n=57) while 33.73% (n=29) cases having solitary stone.

Conclusion: Identification of metaplastic changes of gallbladder carcinoma are important and suggested that every cholecystectomy specimen may be sent to the histopathologist and not be ignored and considered useless.

Key Words: Precancerous lesions, Metaplastic changes, Cholecystitis, Carcinoma gallbladder, Cholecystectomy,

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INTRODUCTION:

Gallbladder cancer (GC), first described by Stoll in 1777¹, is a relatively rare neoplasm and has been considered to be a highly lethal disease. This is the most common biliary tract tumor and the sixth most common malignancy of the gastrointestinal tract². The American Cancer Society has estimated about 10,910 new diagnosed cases and about 3,700 deaths from cancer of the gallbladder and nearby large bile ducts in the United States in the year 2015³. There are no specific clinical symptoms or signs, & most patients have advance disease at presentation.

The minority of GCs are first diagnosed on microscopic examination after routine cholecystectomy for a benign disease.⁴

Compared with other organs of the gastrointestinal tract, the clinical features, morphology, and diagnostic criteria of precursor lesions of the gallbladder and biliary tract are less well characterized.⁵ This is partly because cancerous lesions of the biliary tract are far less common. The relative inaccessibility of the biliary tract is also a contributing factor to advancement in this field.

Precursor lesions of the biliary tract are based on extrapolation of experience gained in other organ systems regarding morphologic signs of dysplasia

The pathologic definition and criteria for precursor lesions of the biliary tract are based on surrogate evidence, such as⁵ common association with malignancy, both spatially and epidemiologically;⁶ anecdotal evidences of progression;⁷ histopathologic similarities to malignancy;⁸ extrapolation of experience gained in other organ systems regarding morphologic signs of dysplasia; &⁹ molecular & genetic evidence of malignant transformation¹⁰.

Although these observations provide an acceptable substrate on which to build criteria, they nevertheless leave room for subjectivity. The clinical features, morphology, and diagnostic criteria of biliary tract precursor lesions are poorly characterized. It has been well established by epidemiologic and clinical studies, however, that the biliary tract is probably the consummate example of inflammation-associated carcinoma. The link between the developments of biliary adenocarcinoma with preceding chronic inflammation has been well established, mostly by epidemiologic data showing a high incidence of gallbladder cancer in areas with a high prevalence of gallstones, and by the pathologic observation that many individual carcinomas have associated gallstones or chronic cholecystitis. Also, the risk of adenocarcinoma is relatively high in patients with primary sclerosing cholangitis (and indirectly with ulcerative colitis).¹¹ The association of biliary cancers with parasitic

infection and choledochal cysts is also, presumably, a reflection of an inflammation-associated carcinoma.

Accordingly, one would assume that these diseases might serve as an opportunity, or a model, to study and characterize carcinogenesis and its precursor lesions. Proper identification of premalignant change in this site is difficult, however, from morphological point of view, the dysplasia-carcinoma sequence is the most plausible carcinogenic pathway for gallbladder cancer.¹² It is believed that most cases of adenocarcinoma are preceded by a sequence of intestinal metaplasia, dysplasia (atypical Hyperplasia) and carcinoma in situ gall bladder.

This is further supported by the fact that intestinal metaplasia is a very common finding in gall bladder mucosa adjacent to an invasive adenocarcinoma as is the finding of carcinoma in situ in the vicinity.¹³ The identification of premalignant modifications in the morphologic background of chronic cholecystitis is an argument in favor of the metaplasia-dysplasia-neoplasia sequence and justifies recent recommendations for the performing of cholecystectomy¹⁴ It has been found that carcinoma GB is usually suspected preoperatively or intraoperatively and histologic analysis does not alter the outcome, therefore some propose that selective microscopic examination of only grossly suspicious GB specimen is the way of the future,¹⁵ however the argument against it is that by doing so precancerous lesions may be missed which usually become evident only upon microscopy.

The current study, on the histopathological observation of frequency of precancerous lesions in the surgically removed gall bladder may reveal that variety of epithelial abnormalities including dysplasia and carcinoma in situ are common lesions.

MATERIAL & METHODS:

The current study was conducted in the department of Histopathology at Pakistan Naval Ship (PNS) Shifa Karachi. 292 cholecystectomy specimens (irrespective of disease) were included and all improperly preserved and autolyzed

samples were excluded from the study. The data was collected by the researcher manually on a proforma.

All the cholecystectomy specimens were fixed in 10% buffered formalin and allowed to stay overnight, then examined grossly for any alteration from normal morphological appearance by the researcher under the supervision of a senior consultant histopathologist. Representative sections were taken, processed and embedded in paraffin as per standard procedure. Four micron thick paraffin sections were cut and stained with hematoxylin and eosin followed by microscopic examination (microscopic description of the slide with diagnosis). Documentation including the hospital identification number, laboratory number, date of receipt of the specimen, patient's age/sex duration of disease, pre operative diagnosis, microscopic description and diagnosis were noted down. Data was analyzed on Statistical Package for Social Sciences (SPSS) version 10.0. Descriptive variables including gross and microscopic lesions encountered were presented by Frequencies and Percentages while the numerical variables such as the age of the patient was computed by Mean +/- Standard deviation. Stratification was undertaken on gender, duration of disease & cause of cholecystitis.

RESULTS:

Table No. 1 shows the distribution of the patients according to their age group, majority of the patients 33.22% (n=97) were recorded between 41-50 years of age, 27.05% (n=79) were found in group 51-60 years, 23.29% (n=68) in 31-40 years age group, while 16.44% (n=48) were found between 20-30 years of age. The mean age was recorded as 42.7± 1.24.

We analyzed gender distribution in the population included in our study, and found 84.25% (n=246) female and 15.75% (n=46) male (Table No. 2).

The table No. 3 shows the status of precancerous lesion(s) which were diagnosed in 86 (29.5%) cases, including squamous metaplastic lesions in 13.01% (n=38), metaplastic intestinal in 8.92% (n=26), dysplastic in 7.53% (n=22) of cases.

Other changes which were not considered as precancerous were found in remaining 70.5% (n=206) of cases, including chronic cholecystitis in 189 cases, eosinophilic cholecystitis in 02 cases. One each case of xanthogranulomatous cholecystitis, follicular cholecystitis, & hyalinizing cholecystitis (porcelain gall bladder) was detected. Cholesterolosis was found in 04 cases. Acute calculous cholecystitis was seen in 03 cases while acute acalculous cholecystitis in 01 case. Acute cholecystitis with mucocele and acute cholecystitis with empyema were diagnosed in two each cases (Table No. 4).

Status of duration of disease was recorded and majority of the patients 51.16% (n=44) gave history of 1-2 years of the disease, 23.25% (n=20) were suffering since 2-3 years while 25.59% (n=22) were having disease since >3 years (Table No. 5).

Table No. 6 describes causes of precancerous lesion among 86 cases. Chronic cholecystitis and cholelithiasis was found in all (100%) cases, while multiple small stones were found in 66.27% (n=57) while 33.73% (n=29) cases were found with single stone.

Table No. 1: Age Distribution of the Subjects (n=292)

Age (in years)	No. of Cases	%
20-30	48	16.44
31-40	68	23.29
41-50	97	33.22
51-60	79	27.05
Total	292	100
Mean & S,D.	42.7±1.24	

Table No. 2: Gender Distribution (n=292)

Gender	No. of Cases	%
Male	46	15.75
Female	246	84.25
Total	292	100

Table No. 3: Status of Precancerous Lesion(s) (n=86)

Lesions	No. of Cases	%
Squamous Metaplastic	38	13.01
Metaplastic Intestinal	26	8.90
Dysplastic	22	7.53
Total	86	29.44

Table No. 4: Status of Other Non-Precancerous Lesion(s) (n=206)

Lesions	No. of Cases	%
Chronic Cholecystitis	189	64.73
Cholestrolosis	04	1.37
Acute Calculous Cholecystitis	03	1.03
Acute Cholecystitis with Mucocele	02	0.68
Acute Cholecystitis with empyeme	02	0.68
Eosinophilic Cholecystitis	02	0.68
Acute Acalculous Cholecystitis	01	0.34
Hyalinizing Cholecystitis (Procelain Gall Bladder)	01	0.34
Xanthogranulomatous Cholecystitis	01	0.34
Follicular Cholecystitis	01	0.34
Total	206	70.53

Table No. 5: Status of Duration of Disease (n=86)

Duration	No. of Cases	%
1-2 years	44	51.16
2-3 years	20	23.25
>3 years	22	25.59
Total	86	100

Table No. 6: Causes of Precancerous Lesions (n=86)

Causes	No. of Cases	%
Chronic Cholecystitis	86	100
Cholelithiasis	86	100
Single Stone	29	33.73
Multiple Small Stones	57	66.27

DISCUSSION:

Carcinoma of the gallbladder ranks fifth in incidence of gastrointestinal carcinomas and represents about three-fourths of extrahepatic biliary tract carcinomas².

The diagnostic imaging study of choice in gallbladder disease is Ultrasonography which can routinely detect gallstones and cholecystitis, however precancerous lesions being both clinically and pathologically are still difficult to diagnose by the technique.

To predict whether a known case of dysplasia will develop into invasive carcinoma is difficult but it does seem to be a morphologically identifiable major candidate as a precursor lesion of the gallbladder carcinoma¹³ because dysplasia encountered in routine Cholecystectomy specimens have been implicated in having similar alterations as found in all stages of gall bladder carcinoma suggesting that such precancerous lesions in fact do have potential and/or tendency to develop into carcinoma at some stage.¹⁶

This study was carried out on the histopathological observation of frequency of precancerous lesions in the surgically removed gall bladder to determine the frequency of precancerous

esions in routine cholecystectomy specimens.

In this series, we found majority of the patients between 41-50 years of age and only 16.44% were found between 20-30 years of age, which shows that cholecystitis is common in elderly age.

Our findings regarding age is in agreement with a study conducted by Mohammad et al¹⁷, who found 45.62 years as the mean age of the patients of acute cholecystitis and confirms that cholecystitis is common in elderly age group.

In our study, we analyzed gender distribution and found majority of the patients as females. These findings are also closely related to same study¹⁷ mentioned above. In this study also, females were found in majority which clarifies that acute cholecystitis is common in females. Another local study conducted by Maratab Ali and colleagues¹⁸ also found an increase incidence of acute cholecystitis in female.

In our findings precancerous lesion(s), squamous metaplastic lesions were found in 13.01% (n=38), metaplastic intestinal in 8.9% (n=26), dysplastic in 7.53% (n=22) and other non-precancerous changes were found in 70.53% (n=206).

According to a study conducted by B Darmas,¹⁹ concluded that all cases of gall bladder carcinoma were suspected pre-operatively or intra-operatively. Histological examination did not alter the management or outcome in any of the cases and suggested that selectively sending specimens for histopathological examination would result in reduced demands on the histopathology department without compromising patient safety while the outcome of this study differ from this point of view because pre-operative and intra operative findings confirm only gall bladder carcinoma and not the precancerous lesions, which are the starting point of gallbladder carcinoma and its identification by histopathologically necessary so that causes and duration of the disease may not be overlooked and timely management may be started. Metaplastic changes are examined and confirmed only on histopathology, so histopathology of every cholecystectomy specimen has gained some space

and it may not be ignored.

Cost effectiveness and workload of histopathologist is also of great importance as indicated in above mentioned study¹⁹ also, but the causes, duration of disease and identification of development of metaplastic changes leading to dysplasia-carcinoma sequence^{20,21} is also of great importance mostly seen in females

CONCLUSION:

Identification of metaplastic changes of gallbladder carcinoma is found to be important and suggested that every cholecystectomy specimen may be sent to the histopathologist and not be ignored and considered useless.

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