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ORIGINAL RESEARCH

Unanticipated Histopathological Presentation of the Cholecystectomy Specimens in a Tertiary Care Hospital: A Five-Year Experience

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ABSTRACT

Background: Gallstones as well as gallbladder cancer are very common in India. North East India also witnesses a large number of gall bladder carcinoma cases. Diagnosis of many unexpected pathologies including incidental carcinoma can only be done on histopathological examination of cholecystectomy specimens. **Objectives**: Our aim is to evaluate the histopathological spectrum of the cholecystectomy specimens done in our hospital and to determine the frequency of Incidental carcinoma along with other uncommon pathologies on histopathological examination of cholecystectomy specimens. **Methods**: This is a retrospective study done in the Department of Pathology, F.A.A.M.C.H., Barpeta, between September 2018 and September 2023. **Results**: Out of 2165 cholecystectomy specimens sent for histopathological examinations 10 specimens (0.46%) were diagnosed as chronic cholecystitis with flat dysplasia, 12 specimens (0.55%) as incidental gall bladder carcinoma and 9 (0.41%) preoperatively diagnosed gall bladder carcinoma specimens were confirmed on histopathological examination. The percentage of Gall bladder carcinoma in cholecystectomy specimen at our hospital is 0.97%. **Conclusion:** Chronic cholecystitis with flat dysplasia and incidental gall bladder carcinoma can be missed in pre and intraoperative periods despite clinical and radiological evaluation preoperatively. So, mandatory histopathological examination of all cholecystectomy speciemens is of utmost importance to avoid misdiagnosis and for early detection of incidental carcinoma.

Key words: Carcinoma, cholecystectomy, histopathology, incidental, dysplasia.

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INTRODUCTION

Gall bladder-related pathologies are not uncommon in our country. Many worldwide studies have shown that India is a high-incidence area for gallbladder stone disease, and this parallels the incidence of incidental gall bladder carcinoma as well. It contributes to about 10% of the global burden of gall bladder carcinoma[1] Certain conditions like lifestyle, dietary habits, micronutrient deficiencies, and environmental risk factors predispose the Indian population more towards gallbladder carcinoma[2]. In India, the incidence of carcinoma gall bladder is estimated to be 22 per 100,000 population.[1] Within India, there is marked variation in the distribution of Gall bladder carcinoma.

Benign gallbladder pathologies like xanthogranulomatous cholecystitis, eosinophilic cholecystitis, porcelain gallbladder, granulomatous lesions like tuberculosis are frequently encountered in the north-eastern part of India. Many of these pathologies are encountered only through histopathological examination of cholecystectomy specimens and significance of these unanticipated alterations is of utmost importance since most findings are challenging to detect in preoperative settings. Failure to detect incidental carcinomas may prove to be disastrous due to its delay in appropriate management.

Our study aims to evaluate the histopathological spectrum of the cholecystectomy specimens done in our hospital. We also want to determine the frequency of Incidental carcinoma and other uncommon pathologies on histopathological examination of cholecystectomy specimens.

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MATERIALS AND METHODS

We retrospectively analysed archived data of all cholecystectomy specimens sent for histopathological examination in the Department of Pathology, F.A.A.M.C.H., Barpeta, between September 2018 and September 2023. Inclusion criteria were all cholecystectomy specimens sent for histopathological examination to the Department of Pathology, F.A.A.M.C.H. The study was approved by institutional ethics committee of Fakhruddin Ali Ahmed Medical College, Barpeta.

The surgically resected cholecystectomy specimens were fixed in 10% neutral-buffered formalin. Required sections from the fundus, body and neck were taken. More representative sections were taken in cases with growth, irregular mucosa, thickened walls, calcification, or necrosis. The sections were then embedded in paraffin, standard procedures were done for the tissue processing, and slides were prepared and stained with Haematoxylin and Eosin stain. Special stains were done whenever required. The gross and microscopic features of all cases were studied in detail.

The collected data from the archives were studied, analysed and presented in tabulated forms.

RESULTS

Our department received 2165 cholecystectomy specimens for histopathological examination between September 2018 and September 2023. Of them, 860 were from male patients, and 1305 were from female.

On histopathological examination, the most common diagnosis was chronic cholecystitis, with a total of 1888 cases (87.2 %), out of which 732 were male and 1156 were female. In many patients, chronic cholecystitis was accompanied by other pathologies as well. 135 (6.23%) patients had chronic cholecystitis with cholesterolosis, 11 patients (0.50%) had chronic cholecystitis with metaplasia, 11 patients (0.50%) had chronic cholecystitis with adenomyomatous hyperplasia, 5 patients (0.23%) had chronic cholecystitis with papillary hyperplasia and 3 patients (0.14%) had chronic cholecystitis with hyalinisation of wall. Acute on chronic cholecystitis was diagnosed in 24 patients (1.11%). Unanticipated findings like xanthogranulomatous cholecystitis were encountered in 34 patients (1.57%), follicular cholecystitis in 13 patients (0.6%), chronic eosinophilic cholecystitis in 2 patients (0.092%) granulomatous gall bladder in 1 patient (0.046%) and chronic cholecystitis with flat dysplasia were seen in 10 (0.46%) cases. Gall Bladder carcinoma was detected in 21 patients (0.97%), of which 3 were male and 18 were female. (Table 1)

Out of the 21 (0.97%) detected cases of gallbladder carcinoma, 9 cases (0.41%) were diagnosed as gallbladder carcinoma preoperatively, and 12 cases (0.55%) were incidental findings.

Table 2 shows the demographic profile, clinical diagnosis and pathological characteristics of the incidental gall bladder carcinoma cases. The mean age of patients with incidental gall bladder carcinoma was 52 years with age ranging from 36-70 years. Female preponderance in the ratio of 11:1 was seen. On gross examination some of the cases showed alteration of normal architecture with findings such as growth in the wall, papillary projections and thickened wall. On histopathological examination, 6 cases showed features of well-differentiated adenocarcinoma, where 2 cases had infiltration up to the perimuscular connective tissue, and 4 had infiltration up to muscularis propria. 6 cases showed histopathological features of moderately differentiated adenocarcinoma, among which 4 had infiltration up to the perimuscular connective tissue, and 2 had infiltration up to the muscular propria. 2 cases (1 well-differentiated adenocarcinoma and 1 moderately differentiated adenocarcinoma) had perineural invasion as well. (Table 2)

Table 3 shows the demographic profile, clinical diagnosis and pathological characteristics of the preoperatively diagnosed gall bladder carcinoma cases. The median age is 56 years, with an age range of 45-70 years showing a female preponderance. The common gross findings were thickened gall bladder wall, growth with papillary projections. 6 cases showed histopathological features of well differenciated adenocarcinoma among which 4 had infiltration upto perimuscular connective tissue, 1 had infiltration upto muscularis propria and 1 had infiltration beyond serosa. 1 case showed histopathological features of moderately differentiated adenocarcinoma invading upto perimuscular connective tissue. 1 case showed histopathological features of poorly differentiated adenocarcinoma with infiltration beyond serosa. 1 case was diagnosed as mucinous adenocarcinoma with infiltration beyond serosa. (Table 3)

	SL. No	Pathology	Number of cases	%	Male	Female
1. Non-NeoplasticConditions	**1.**	**Acute**				
		Acute on Chronic Cholecystitis	24	1.11	9	15
		Empyema	4	0.18	2	2
	2.	**Chronic**				
		Chronic Cholecystitis	1888	87.2	732	1156
		Chronic Cholecystitis with Metaplasia	11	0.50	2	9
		Chronic Cholecystitis with	135	6.23	76	59

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		Cholesterolosis				
		Chronic Cholecystitis with hyalinisation of wall	3	0.14	2	1
		Chronic Cholecystitis with Papillary Hyperplasia	5	0.23	3	2
		Xanthogranulomatous Cholecystitis	34	1.57	15	19
		Follicular Cholecystitis	13	0.6	4	9
		Chronic Eosinophilic Cholecystitis	2	0.092	1	1
		Porcelain Gall Bladder	2	0.092	0	2
	3.	**Other Inflammatory conditions**				
		Granulomatous inflammation of GB	1	0.046	1	0
		Mucocele	1	0.046	0	1
Tumour & Tumour like conditions	**1.**	**Flat/Nontumoral preinvasive lesions**				
		Chronic Cholecystitis with Flat Dysplasia	10	0.46	5	5
	2.	**Benign tumour and tumour like conditions**				
		Chronic Cholecystitis with Adenomyomatous Hyperplasia	11	0.50	5	6
	3.	**Malignancy**				
		Adenocarcinoma	21	0.97	3	18
Total			2165	100	860	1305

Table 1: Histopathological spectrum of cholecystectomy specimens

Sl. no.	Age	Sex	Clinical diagnosis	Gall stones	Gross findings	Histopathological diagnosis
1.	55 years	Male	Chronic Cholecystitis	Present	Growth in wall	Moderately differentiated adenocarcinoma infiltrating up to perimuscular connective tissue.
2.	70 years	Female	Empyema gall bladder	Absent	Growth in wall	Moderately differentiated adenocarcinoma infiltrating up to muscularis propria.
3.	55 years	Female	Cholelithiasis	Present	Thickened wall	Well-differentiated adenocarcinoma infiltrating up to perimuscular connective tissue.
4.	50 years	Female	Cholelithiasis	Present	Multiple tiny papillary projections are in the fundus and body. Wall thickened.	Well-differentiated adenocarcinoma infiltrating up to muscularis propria.
5.	60 years	Female	Cholelithiasis	Present	Thickened wall	Moderately differentiated adenocarcinoma Infiltrating up to Muscularis Propria.
6.	40 years	Female	Cholelithiasis	Present	Anatomy distorted. Blackish areas noted.	Well-differentiated adenocarcinoma Infiltrating upto perimuscular connective tissue.
7.	59 years	Female	Chronic calculous cholecystitis	Present	Wall thickened	Moderately differentiated adenocarcinoma infiltrating upto perimuscular connective tissue.
8.	45 years	Female	Cholelithiasis	Present	Anatomy distorted. Whitish growth noted	Moderately differentiated adenocarcinoma infiltrating

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					(3x 0.8) cm in G.B. wall	uptoperimuscular connective tissue.
9.	36 years	Female	Chronic calculous cholecystitis	Present	Wall thickened. Whitish growth noted (1.5x 1) cm in G.B. wall	Moderately differentiated adenocarcinoma invading peri muscular connective tissue with perineural invasion.
10.	59 years	Female	Chronic calculous cholecystitis	Present	Thickened area (1.1x1) cm in G.B. wall. Mucosa flattened.	Well differentiated adenocarcinoma infiltrating upto Muscularis Propria.
11.	60 years	Female	Cholelithiasis	Present	Wall thickened. Whitish growth (1.3x0.8) cm in G.B. wall	Well differentiated adenocarcinoma invading peri muscular connective tissue with perineural invasion.
12.	40 years	Female	Multiple polyps	Absent	Thickened wall and Mucosal elevations at places.	Well differentiated adenocarcinoma infiltrating upto muscularis propria.

Table 2: Characteristics of incidental gall bladder carcinoma

Sl. no.	Age	Sex	Clinical diagnosis	Gall stones	Gross findings	Histopathological diagnosis
1.	45 years	Female	Carcinoma gall bladder	Absent	Wall thickened. White mass noted in wall measuring (3x0.8)	Moderately differentiated adenocarcinoma invading up to perimuscular connective tissue.
2.	45 years	Female	Gall bladder mass	Absent	Papillary projections noted on the mucosa	Well differentiated adenocarcinoma invading up to perimuscular connective tissue.
3.	70 years	Female	Cholecysto-duodenal fistula with Carcinoma gall bladder	Absent	Wall thickened.	Poorly differentiated adenocarcinoma infiltration beyond serosa.
4.	53 years	Female	Carcinoma Gall bladder	Absent	Wall thickened	Well differentiated Adenocarcinoma infiltrating beyond serosa
5.	52 years	Female	Carcinoma Gall Bladder	Absent	Wall thickened	Well differentiated Adenocarcinoma infiltrating up to perimuscular connective tissue.
6.	65 years	Female	Carcinoma gall Bladder	Absent	Wall thickened	Mucinous Adenocarcinoma infiltrating beyond serosa.
7.	52 years	Female	Carcinoma Gall Bladder	Absent	Papillary-like projections noted on the mucosa. Wall Thickened.	Well differentiated adenocarcinoma invading up to perimuscular connective tissue
8.	65 years	Male	Carcinoma Gall Bladder	Absent	Wall thickened	Well differentiated adenocarcinoma invading up to perimuscular connective tissue.
9.	45 years	Female	Carcinoma Gall Bladder	Absent	Wall thickened	Well differentiated adenocarcinoma extending up to muscularispropria.

Table 3: Characteristics of preoperatively diagnosed gall bladder carcinoma

DISCUSSION

The pathogenesis of gallbladder diseases and gallbladder carcinoma is a multi-step process in which genetic and epigenetic alterations accumulate due to host and environmental factors.[3] The pathogenesis of gallbladder carcinoma in Indian setting, including the risk factors of gall stones causation (Asian ethnicity, family history, high fat/low protein diet, micronutrient deficiency, etc.) showed that a combination of multiple factors may act in tandem to promote

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carcinogenesis.[3] In the report titled, 'Profile of Cancer and Related Health Indicators in the Northeast Region of India, 2021' published by the I.C.M.R., which included cancer data between 2012-2016, compiled by 11 P.B.C.R.s (population based cancer registries) in all the 8 Northeastern states and 7 H.B.C.R.s (hospital based cancer registries) in 4 states (Assam, Manipur, Mizoram and Tripura) the highest A.A.R.(age adjusted incidence rate) for gallbladder Carcinoma among Northeastern states was observed in Kamrup urban district for females and Cachar being 2nd highest for both the genders. The same report showed that across the Northeastern states gallbladder is the third most common site among females for cancer (7.1%) right after breast, cervix and uterus.[4]

Our study shows the spectrum of lesions found in the histopathological analysis of the cholecystectomy specimens. The most common diagnosis on histopathological examination was chronic cholecystitis. Of all the 21 occurrences of gallbladder carcinoma, 11 were incidentally detected, and out of that, 10 involved female patients solely. Most gallbladder carcinoma cases were in the 50 - 60 age range. Females had an overall high predominance of developing many gall bladder diseases, including malignancy.

About 87.2% of cases in our study had chronic cholecystitis which is similar to studies by Kumbhakar et al. (86.25%)[5] and Hajong R et al.(70.47%)[6]. In our study, 135 cases (6.23%) of chronic cholecystitis were associated with cholesterolosis, which is very similar to the study done by Kumbhakar *et al.* (7.50%).[5] There were 11 cases (0.50%)of chronic cholecystitis associated with adenomyomatous hyperplasia and 5 cases (0.23%) of chronic cholecystitis associated with papillary hyperplasia. Other significant benign findings were that of empyema (4 cases, 0.18%), mucocele (1 case, 0.04%) and Granulomatous inflammation (1 case, 0.04%).

In our study, we found 2 cases of porcelain gallbladder and 3 cases of chronic cholecystitis with wall hyalinisation. According to a study done by Samip Patelet al hyalinising cholecystitis is a distinct histopathologically defined form of cholecystitis with minimal or no calcifications (incomplete porcelain gall bladder) and the carcinomas arising from this group are often very subtle and prone to misdiagnosis microscopically.[7]

Certain pathologies can mimic malignancy, such as Xanthogranulomatous Cholecystitis. Adjacent organ involvement is also commonly seen in this entity due to the spread of inflammation to surrounding organs. In addition, wide variation in the morphological features also adds to the difficulty in differentiating from malignancy.[1] A study by Rammohan et al. mentionedthat the incidence of Xanthogranulomatous Cholecystitis in India ranges from 0.7 to 10%.[8] In our study we observed 34(1.57%) cases of Xanthogranulomatous Cholecystitis, 15 male and 19 female patients.

Follicular Cholecystitis is another infrequent entity which might be mistaken for lymphoma on morphology[9]. In a study done by Mohan H et al[10]in North India, the percentage of follicular cholecystitis cases was 2.3%. In our study the percentage of follicular cholecystitis cases was 0.59 % which is similar to the study done by Sabina et al.[11]

Eosinophilic cholecystitis may either be seen as a single entity or may coexist with other conditions, eosinophilic gastroenteritis, eosinophilic cholangitis, eosinophilia-myalgia syndrome, idiopathic hypereosinophilic syndrome, parasitic infestations such as Clonorchis sinensis and hydatid cyst and antibiotics like erythromycin and cephalosporins. Therefore once the diagnosis of eosinophilic cholecystitis is made histopathologically, it is very important to identify the underlying aetiology and to exclude other organ involvement.[12] The incidence of eosinophilic cholecystitis is very low in India and is prevalent in 0.25-6.4% of all cholecystitis.[13] In our study, only 2 cases (0.092 %) of eosiniphiliccholecystitis was noted.

There are two essential carcinogenesis models known: the metaplasia-dysplasia-carcinoma sequence and the adenoma-carcinoma sequence. Several studies have also reported an association between pyloric metaplasia and dysplasia, pyloric metaplasia and cancer and an association between intestinal metaplasia and pyloric metaplasia, dysplasia and cancer. [14]Gallbladder dysplasia can progress to gall bladder carcinoma and other pancreato-biliary malignancies.[15]

Our study found 11 cases of chronic cholecystitis associated with metaplasia (0.5%). A Similar Percentage of metaplasia was seen in a study done by Sabina et al.[8] and a study from the Middle East by Zahrani et al. [16] Metaplastic changes occur focally along with chronic cholecystitis and sometimes are not reported by pathologists. A meticulous search for metaplasia may increase the incidence of metaplastic changes while reporting chronic cholecystitis cases.

There were 10 cases (0.46%) of chronic cholecystitis associated with flat dysplasia in our study. In cases of chronic cholecystitis with flat dysplasia thorough sampling of the specimen is necessary to rule out underlying invasive tumour. In a study done by Khosiol Jill et al[15], in 140 cholecystectomy specimens in a region of Chile, gall bladder dysplasia without cancer was found in 14 patients and dysplasia with cancer in 3 patients. In a study by Davide et al.[17], the incidence of dysplasia was found to be 0.6%, almost similar to our study. Gallbladder dysplasia can progress to gallbladder carcinoma and other pancreato-biliary malignancies.

Despite not being a precursor, some lesions like gallbladder polyp increase the risk of gallbladder cancer.[18] In our study, one case clinically diagnosed as multiple polyps, on histopathological examination

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showed presence of well-differentiated adenocarcinoma infiltrating up to muscularis propria.

The incidence of Incidental gall bladder carcinoma is different in various parts of India. The population based cancer registry set up by I.C.M.R provides data of gall bladder carcinoma incidence of Kamrup Urban, Cachar, Dibrugarh and Karimganj. In our study the percentage of Gall bladder carcinoma in cholecystectomy specimen at our hospital is found to be 0.97% which is similar to studies done by Kalita D et al[14] and Sharma, J et al[19]. The incidence of Incidental gallbladder carcinoma is found to be of 0.55% in our study which is comparable to other studies. (Table 4)

Serial no	Author	year	Incidental gall bladder carcinoma (%)	Place of study
1	Jetley Sujata et al[20]	2013	0.96%	North India
2	Sharma, J. et al[19]	2014	1.9%	Eastern India (Assam)
3	Bhanu Pratap Singh et al [21]	2020	0.51%	New Delhi, India
4	Poudel R et al [22]	2020	1.67%	Nepal
5	Yadav R et al[23]	2021	1.26%	North India
6	Di Mauro D et al [17]	2021	0.1%	UK
7	Biswanath Paul et al[24]	2022	2.8%	Eastern India (west Bengal)
8	Our study	2024	0.55%	Barpeta district, Assam

Table 4: Incidence of incidental gall bladder carcinoma in comparison to others

CONCLUSION

As gall bladder pathologies are common in our region, histopathological examination is essential in all cholecystectomy specimens. Preoperative investigations may suggest benign or malignant conditions, but they cannot definitively differentiate between them many a times. Amongst the unanticipated pathologies in our study, chronic cholecystitis with flat dysplasia and incidental carcinoma are the most challenging. Due to rising trend of gall bladder carcinoma early diagnosis of these conditionsby histopathological examination are of great importance for further management planning.

LIMITATIONS

This study is a single institutional retrospective study done in medical college of Barpeta District, Assam. In addition Barpeta District has one Cancer care centre and many private hospitals. A multricentric prospective database in Barpeta district, Assam will reflect the actual incidence of incidental gallbladder carcinoma and preoperatively diagnosed gallbladder cases in this region.

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