Original Article

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Incidental Detection of Precancerous and Malignant Gall Bladder lesions in routine cholecystectomy specimens- A retrospective study of 3 years

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ABSTRACT

Background & Objectives: Gallbladder dysplasia (GBD) and adenoma are premalignant lesions, which may progress to carcinoma through different pathways. Gall bladder (GB) neoplasms are relatively uncommon and are usually asymptomatic during early stages. We analyzed the clinico-pathological features of precancerous and malignant gallbladder lesions in routine cholecystectomy specimens and studied the association of mucosal metaplasia and gall stones with GB adenoma, dysplasia and carcinoma.

Materials & Methods: This is a 3 year retrospective study where histopathology proven cases of GBD, adenomas and carcinomas were retrieved from Pathology database from January 2012 to December 2014. The clinical details and histopathological features of these cases were studied and analyzed.

Results: Out of total 2200 cholecystectomy specimen studied, 7 cases of GBD, 5 cases of adenoma and 10 gallbladder carcinomas (GBC) were identified. Out of total 22 patients, 11 were females. Predominant clinical feature was pain in 86% cases. On ultrasonography (USG), majority showed cholelithiasis. Cholecystectomy was performed in all predominantly due to cholecystitis and lithiasis. On microscopy, 43% cases of dysplasia showed high grade features, 60% cases of adenoma showed tubular type with pyloric metaplasia and 50% of GBC were moderately differentiated. Associated dysplasia in GBC was noted in 50% and associated metaplasia in 60% cases. Follow up ranged from 2-4.5 years. 40% GBC showed lymph node involvement and 20% showed distant metastasis.

Conclusion: All cholecystectomy specimens should definitely be sent for histopathologic evaluation to detect unapparent GB lesions. Early detection of these lesions may lead to good prognosis and prolonged survival.

Keywords: *Cholecystectomy, Gall Bladder, Incidental, Lesio*

Introduction

Gall bladder lesions are relatively uncommon and often pose a diagnostic dilemma. 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. [(1)] In gallbladder epithelium adjacent to invasive carcinoma, dysplasia is noted in 40 - 60% of cases and in about 1% of all elective cholecystectomies done because of gallstones, an occult GB cancer was detected. Carcinoma of gallbladder is an aggressive malignancy and usually presenting at an advanced stage. [(2)] Different carcinogenic models involved in the evolution of gall bladder malignancies have been proposed involving dysplasia and adenomas. GBC is the most common malignancy of the biliary tract and accounts for 3% of all tumors. [(3)] It is characterized by a rapidly progressive course with a high mortality rate. As far as etiopathogenesis is concerned, gallstones, chronic inflammation, presence of adenomas, dysplasia and other risk factors such as gender, age, obesity and parity have been implicated. Strong correlation between GB stones and GBC have been suggested in the literature. [(3)] Early stages of GBC are usually asymptomatic or present with symptoms similar to chronic cholecystitis. A preoperative diagnosis of GBC is usually seen in cases of advanced tumors which have infiltrated adjacent organs. [(4)] According to WHO, incidental detection of gall bladder carcinoma (IGBC) refer to the cases of GBCs which are not suspected before and during surgery, and not even on gross examination of the opened GB specimen. The diagnosis is made for the first time on histopathological examination. Prognosis of IGBC is better as compared to symptomatic GBC due to its detection at early stage.

In this study we analyzed the clinico-pathological features of precancerous and malignant GB lesions in routine cholecystectomy specimens and also study the association of mucosal metaplasia and gall stones with these GB lesions.

Materials and Methods

This is a retrospective study of three years conducted in a tertiary care hospital at Southern India. All 2200 cases of cholecystectomy were retrieved from Pathology

databases from January 2012 to December 2014. Twenty two histopathology proven cases of incidental GBD, adenomas and carcinomas were selected for this study. Gross specimens of GB were processed in our laboratory according to standard protocol which includes opening of the specimen, fixation and extension on paraffin blocks and thorough examination of suspicious lesions. Subsequently, 3 representative samples from the head, body and fundus of the gallbladder were submitted for histological analysis. Clinical and pathological details of all these cases were studied and analyzed.

Results

Out of 2200 cholecystectomy specimens studied, 7 cases of GBD, 5 cases of adenoma and 10 GBC were identified (Table 1). Incidence of GBD, adenoma and carcinoma in our study period was 0.318%, 0.22% and 0.44% respectively. Out of total 22 patients, 11 were females and their age ranged from 19 to 70 years. The predominant clinical features for these cases were pain (86%), vomiting (27%) and fever (18%). On USG, 68% of cases showed cholelithiasis and 22% thickened wall (Table 1). Cholecystectomy in majority of cases was performed due to cholecystitis and lithiasis. Fifty percent cases of GBC and 28.6% cases of dysplasia presented as cholelithiasis with acute cholecystitis. Chronic chokecystitis was the presenting symptom in 60% cases of adenomas, 71% cases of dysplasia and 50% cases of GBC. On gross examination, 9 cases showed polypoidal nodule and 5 had wall thickening. On microscopic examination, the histological spectrum included epithelial metaplasia, dysplasia, adenoma and carcinoma. Four of the seven (57%) cases of dysplasia showed low grade while 3/7 (43%) cases showed moderate to high grade features (Fig 1-3) (Table 1). Three of five (60%) cases of adenoma were tubular type with pyloric metaplasia and among these 40% had associated dysplasia (Fig 4). Five of the 8 (62.5%) cases of GBC showed moderate differentiation (Fig 5)(Table 1). One case each of signet ring cell adenocarcinoma (Fig 6) and adenosquamous carcinoma was reported. Associated dysplasia and metaplasia were noted in 50% and 60% cases respectively. Follow up period ranged from 2-4.5 years. Four of the ten GBC cases (40%) cases showed lymph node involvement and 50% of them received chemotherapy according to 8th AJCC TNM staging. These cases had no recurrence in the follow up period. 2/10 cases showed distant metastasis and did not pursue further treatment due to financial constraints. 4 cases were lost on follow up.

Discussion

The incidence of detection of premalignant lesions of GB in routine histopathological examination of cholecystectomy specimens has been increased. High grade dysplasia is reported in 1 to 3.5% of cholecystectomies performed and low grade dysplasia in up to 15% in areas of world with high incidence of GBC, whereas adenomas are detected in <1% of cholecystectomies performed. [3] GBC has rapid progression with high mortality rate and reported as most common cancer of biliary tree. According to the literature,

Table 1: Demographic, clinical and morphological features of adenomas, dysplasia & carcinoma of gallbladder.

	ADENOMAS (N=5)	ISOLATED DYSPLASIA (N=7)			CARCINOMA (N=10)		
		LOW (n=4)	MODERATE (n=2)	SEVERE (n=1)	ADENOCA. NOS(n-=3)	MOD. DIFF. ADENOCA (n=5)	OTHER TYPES (n=2)
INCIDENCE	0.22		0.31			**0.44**	
M:F	2:3	3:1	2:0	F	**2:1**	**2:3**	**1:2**
MEAN AGE(YRS)	46	35	48	63	**57**	**62**	**58**
ASSOCIATED CHOLELITHIASIS	3/5	4/4	2/2	+	**2/3**	**5/5**	**2/2**
GROSS:LOCALISED GROWTH	4/5	--	THICKENED WALL	--	POLYPOIDAL-3	POLYPOIDAL-3 FLAT- 2	FLAT-1/2
ASSOCIATED METAPLASIA	2/5	3/4	--	GASTRIC	**3/3**	**4/5**	**--**
DYSPLASIA	2/5	4/4	2/2	SEVERE	**3/3**	**3/5**	**--**
CHOLESTEROLOSIS	1/5	--	FOCAL	--			
ACUTE CHOLECYSTITIS	--	--	2/2	--	**1/3**	**3/5**	**1/2**
CHRONIC CHOLECYSTITIS	3/5	4/4	--	+	**1/3**	**3/5**	**1/2**
METASTASIS	--	--	--	--	**2/3**	**2/5**	**2/2**

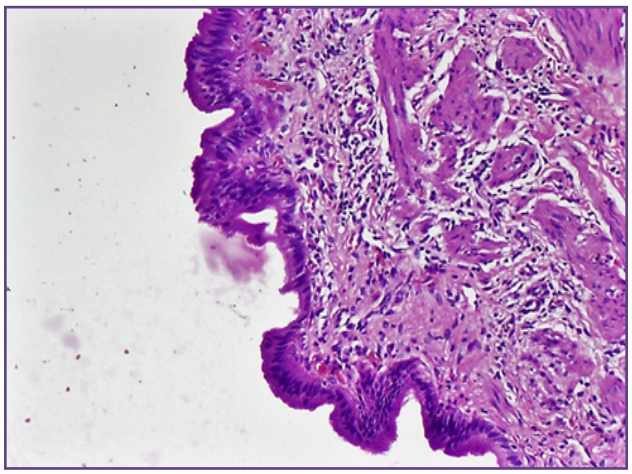

Fig.1: H&E 100X; Low grade GB dysplasia with nuclear pseudostratification and mild hyperchromasia

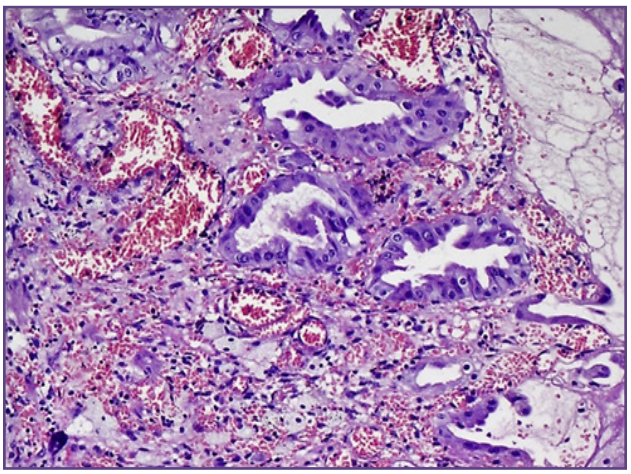

Fig.2: H&E 100X; Irregular glands showing moderate dysplasia with associated cholesterolosis.

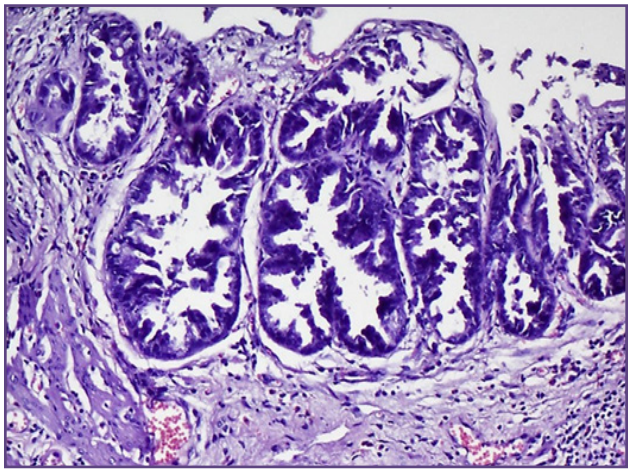

Fig. 3: H&E 100X; Irregular and star shaped glands showing severe GB dysplasia.

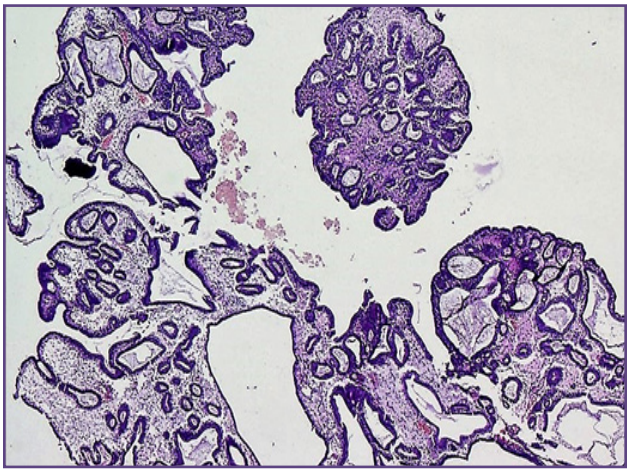

Fig. 4: H&E 40X; Tubulo-papillary adenoma with associated low grade dysplasia.

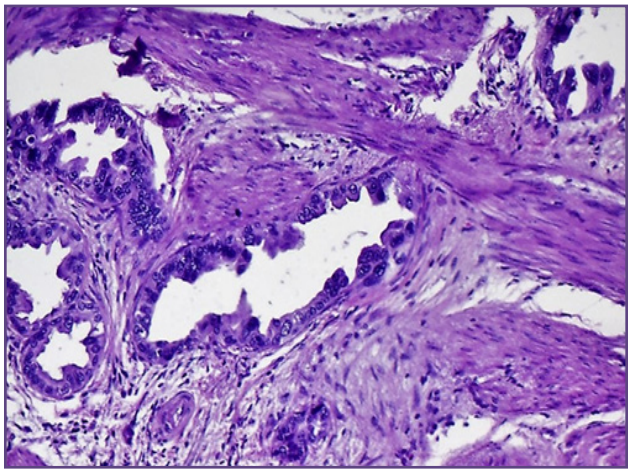

Fig. 5: H&E 100X; Moderately differentiated adenocarcinoma infiltrating the underlying muscularis layer

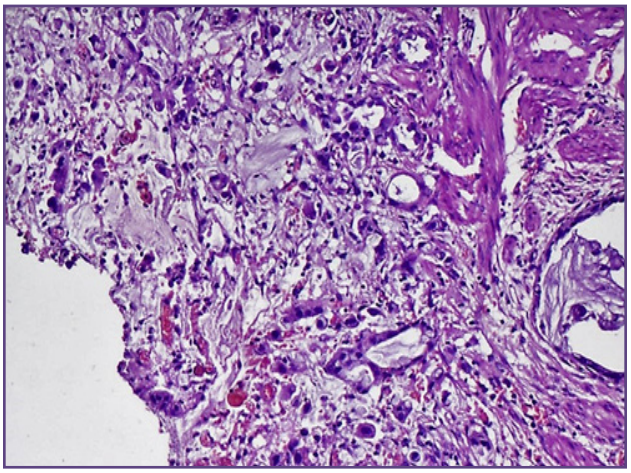

Fig. 6: H&E 100X; Signet ring cell adenocarcinoma seen infiltrating the muscularis layer.

incidence of IGBC has been varied from 0.3-2% and our study is no different with reported incidence of 0.46. [3,6] However, our reported incidence is less in comparison to studies done by Cavallaro et al and Bhawna et al. [4,6] GBC shows female predominance affecting individual in sixth and seventh decade [4,5,6] and we also found similar predilection and age profile with mean age of presentation of being 59 years.

Gallstone has always been considered as an important risk factor for GBC however this causal relationship has yet to be established. In our study 90% cases of GBC had associated gall stones, as observed by other authors. [3-7] Bhawna et al in their study have also illustrated that GB dysplasia, tubular adenomas, carcinoma in situ and invasive carcinoma were frequently associated with gall stones. Very few lesions were found to have no associated cholelithiasis. [6] Similarly, Gupta et al. [7] also found high prevalence of gall stones in all GB lesions. In concordance with the literature, we found gallstones in 3 of the 5(75%) cases of GB adenomas, 100% cases of isolated dysplasia and 9 of the 10(90%) cases of GBC. Three cases of GBC and one case each of GB adenoma and low grade dysplasia showed associated brown or black pigment stones, however this feature is not well documented in literature for comparison and analysis. We found majority of GBC cases (90%) presented with acute or chronic cholecystitis with cholelithiasis which was also observed by Kamble et al. [8] where 80.5% cases had similar presentation.

Although the pathogenesis of gallstones causing GBC is not well understood, it has been suggested that constant chronic irritation and inflammation due to gallstones lead to the epithelial changes like ulceration, metaplasia and dysplasia in the gall bladder mucosa finally leading to GBC. There are two models to explain this malignant transformation of the precursor lesions: the dysplasia–carcinoma sequence and the adenoma–carcinoma sequence. [6,9] According to morphology, the dysplasia–carcinoma sequence is more acceptable in comparison to the other, probably due to lower frequency and the absence of adenomatous component in the GB mucosa in early carcinoma cases. On the contrary, the histologic spectrum from dysplasia to the carcinomas in situ, associated with invasive GBC, are more frequent finding in the GB mucosa adjacent to the tumors, thus favouring the former model [6,9]

GBC in its early stages is difficult to diagnose clinically and on radiology. On USG, about 40-60% cases are detected only when a solid intraluminal mass is present.[7] Diffuse GB wall thickening is considered as a non-specific finding which can be observed even in chronic inflammatory conditions. [10] In present study 40% cases showed diffusely thickened wall on radiological examination.

On histological examination, we found associated dysplasia in 6 of the 10(60%) cases of GBC in the adjacent or superficial mucosa, however, such association has been documented by other authors as well.[6,11] We noted associated metaplasia was noted in 7 out of 10 (70%) GBC cases, with similar results mentioned by Saavedra et al. [11] where metaplastic changes were noted in 78% cases of GBC. Study by Bhawna et al. [6] reported associated metaplasia, predominantly intestinal metaplasia in 90% cases of GBC. Such high percentage may suggest definite close association between metaplasia, dysplasia and carcinoma. However, we had found antral metaplasia more frequently in present study. We also analyzed metaplastic changes in cases of GB dysplasia and found this feature associated in 57% cases of dysplasia, similar to the study by Bhawna and co-workers. [6]

Although cholesterolosis is not been considered as a premalignant condition, but in our study it has been found associated with one case each of adenoma and dysplasia. Similar observation was noted in another study where cholesterolosis was documented in 5 cases of dysplasia and one case of GBC [6] Adenocarcinomas are the most frequent histological subtype of the malignant GB neoplasms forming 90-95% of all cases. [3,6,14] In concordance with the literature our study also showed incidence of adenocarcinoma in 90% of cases of GBC. Authors Dowling et al [12] and Kwon et al [13] also had similar results and reported adenocarcinoma as most frequently encountered GBC seen in 86 % and 100% cases respectively in their studies.

At present, simple cholecystectomy is considered an adequate therapy for early GBC and radical operation should be carried out in advanced stage of disease to improve the prognosis of patients. [13] As a standard protocol, in all cases of adenoma, dysplasia and GBC simple cholecystectomy is performed. It has been documented that incidentally detected GBC are surgically resectable with good overall survival. [14,15] On follow up, our study had 40% cases GBC with lymph node involvement, similar results were also noted by Cavallaro et al. [4] with 42% cases with lymph node involvement. However, Ghnnam etal [5] found only 20% lymph node involvement in their study.

Conclusion

Detection of gallbladder lesions in routine cholecystectomy specimens, in the absence of clinico-radiological suspicion, emphasizes the importance of a careful histopathological examination of all cholecystectomy specimens. The observation of histopathological features reveal a relationship between gall stones, premalignant and malignant conditions of GB. Since adenoma and dysplasia are known precursor lesions for invasive carcinomas, a

vigilant microscopic examination is warranted to enable early diagnosis and prompt treatment. Essentially, GB can be considered as a hidden graves for premalignant and malignant lesions and therefore, all cholecystectomy specimens should be thoroughly sampled and examined on microscopy for occult malignancies.

Take Home Message

1. Gallbladder can be considered as hidden graves for premalignant and malignant lesions. Therefore, all cholecystectomy specimens should be thoroughly sampled for occult malignancies.
2. Since adenomas and dysplasias are known precursor lesions for invasive carcinomas, a vigilant microscopic examination is warranted to enable early diagnosis and prompt treatment.
3. Morphological examination reveal the relationship between gallstone and gallbladder lesions.

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