Research Paper

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Routine Histopathologic Examination Of Cholecystectomy Specimens – Role In Detection Of Epithelial Neoplasms Of The Gall Bladder

Pathology

KEYWORDS : gall bladder, carcinoma, adenoma, dysplasia, cholecystectomy.

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ABSTRACT

Introduction: Adenomas and dysplasias of the gall bladder are premalignant lesions which have been proposed to progress to carcinoma through different pathways. There is an increase in the incidence of detection of these lesions in routine cholecystectomy specimens. This study was carried out to study the clinicopathologic characteristics of gall bladder epithelial neoplasms.

Materials and methods: A retrospective study of all patients diagnosed with adenoma, dysplasia and carcinoma in a tertiary care hospital between September 2011 and September 2014 was done. The clinical and histopathological features were studied.

Results: Twenty four cases of gall bladder neoplasms were studied with 5 cases of adenoma, 7 cases of dysplasia and 12 cases of carcinomas. The indication for cholecystectomy for majority of these patients was chronic cholecystitis associated with gall stones. The most common type of adenoma noted was tubular type with pyloric metaplasia and few were also associated with dysplasia. Dysplasia was seen in half of the patients with invasive cancers while no adenoma was noted.

Conclusion: The presence of dysplasia in the mucosa adjacent to cancers, support the causal relation of dysplasia and carcinoma in the gall bladder. This further highlights the need for detection of high risk patients for early diagnosis of gall bladder neoplasms and prophylactic cholecystectomy.

INTRODUCTION:

Gall bladder epithelial neoplasms are relatively uncommon and include premalignant lesions like adenoma and dysplasia, and carcinomas. Different carcinogenic models involved in the evolution of gall bladder malignancies have been proposed involving dysplasias and adenomas. (1)

Carcinoma of the gall bladder is associated with rapid progression and a high mortality rate. (2)Preoperative diagnosis of gallbladder cancer is uncommon, with the exception of advanced tumors which have infiltrated adjacent organs.(3) Majority these epithelial neoplasms are detected on histopathological examination of a gall bladder removed for presumed diagnosis of gallstone disease or cholecystitis with the incidence ranging from 0.3–1.5% .(1)Though the prognosis of gall bladder cancer is poor, early detection and prompt treatment is associated with better outcomes. The present study was done to analyse the clinico-pathologic features of gall bladder epithelial neoplasms.

MATERIALS AND METHODS:

A restrospective study was conducted in a tertiary care hospital during a three year study period between September 2011 and September 2014 on all cases of gall bladder neoplasms. These included adenomas, dysplasias and carcinomas, diagnosed on histopathologic examination of cholecystectomy specimens. . The medical records of all patients were reviewed for their presenting features, clinical diagnosis, radiological investigations and follow up. The gross specimen and histopathology slides were reviewed with special reference to presence of associated changes in adjacent mucosa such as metaplasia and features of cholecystitis. The data obtained was thus tabulated and studied.

RESULT

Twenty four cases of gall bladder neoplasms were retrieved which included adenomas (5/24), isolated dysplasias (7/24) and invasive carcinomas (12/24), the clinicopathologic features of which are demonstrated in tables 1, 2 and 3.

Table 1: Clinicopathologic characteristics of adenomas (n=5)

Male:Female (M:F)	**2:3**
Mean age (yrs)	**46**
Clinical diagnosis of chronic cholecystitis	**2**
Gross	
Localised growth	**4**
Gall stones	**3**
Gross	
Polypoid lesion	**4**
Microscopy	
Tubulopapillary type adenoma	**1**
Papillary type adenoma	**1**
Tubular, pyloric type adenoma	**3**
Metaplasia	**2**
Dysplasia	**2**
Chronic cholecystitis	**3**

Five cases of adenoma (Figure 1) were identified with age range of 28 to 55 years. Majority presented with pain abdomen (4/5) while one had easy fatigability. Biliary sludge and calculi were seen in three cases and one case showed a polyp on ultrasonography. The clinical diagnosis was polyp (2/5) and chronic calculous cholecystitis (2/5). The clinical detail of one case was not available. Grossly, polypoidal growth ranging from 0.5 to 2.5 cm in diameter, were visible on cholecystectomy specimens in four cases. Two cases showed mild dysplasia, of which one also had spindle cell metaplasia in the adjacent mucosa. Cholesterolosis

and gastric metaplasia was also detected in one case.

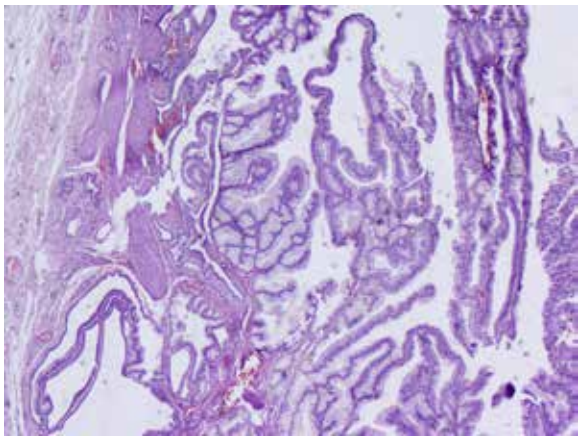

Figure 1: Photomicrograph showing tubulopapillary adenoma with pyloric gland metaplasia. (H&E X2x)

Table 2: Clinicopathologic characteristics of dysplasias (n=7)

Grade	mild (n=4)	moderate (n=2)	severe (n=1)
M:F	3:1	2:0	0:1
Mean age (years)	35	48	63
Clinical diagnosis of chronic cholecystitis	4	2	1
Gross			
Localised growth	0	0	1
Gall stones	4	2	1
Microscopy			
Metaplasia	3	0	1
Adenoma	0	0	0
Acute cholecystitis	0	2	0
Chronic cholecystitis	4	0	1

All the seven cases of dysplasia (Figure 2) were in the age range of 24 to 67 years, presented with abdominal pain and revealed calculi on radiology. They were proferred a clinical diagnosis of chronic calculous cholecystitis. None of the cases showed any lesion on gross inspection of the gall bladder. One case of moderate dysplasia had thickened wall. On microscopy, three cases showed gastric metaplasia and none of them had associated adenomas.

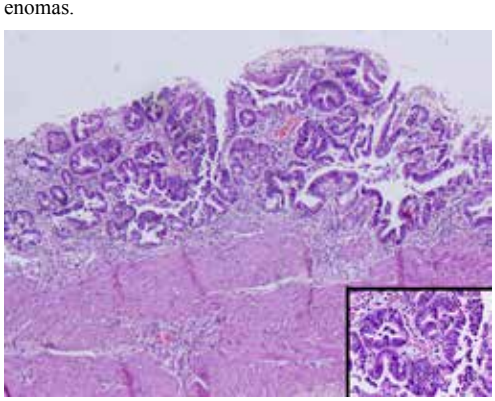

Figure 2: Photomicrograph showing severe dysplasia of the lining epithelium and glands (H&E X2x). Inset: Epithelium and glands lined by dysplastic cells with loss of nuclear polarity and hyperchromasia. (H&E X20x)

Table 3: Clinicopathologic characteristics of carcinomas (n=12)

TYPE	Adenocarcinoma (not otherwise specified) (n=10)	Signet ring cell adenocarcinoma (n=1)	Adenosquamous carcinoma (n=1)
M:F	6:4	0:1	0:1
Mean age (years)	52	64	57
Clinical diagnosis			
Malignancy	5	1	0
Acute cholecystitis	2	0	0
Chronic cholecystitis	3	0	1
Metastasis	5	1	0
Gross			
Flat lesion	3	1	0
Polypoidal growth	7	0	1
Gall stones	5	1	0
Microscopy			
Metaplasia	7	0	0
Dysplasia	6	0	0
Adenoma	0	0	0
Acute cholecystitis	4	1	0
Chronic cholecystitis	3	0	1

Of the 10 cases of adenocarcinoma, not otherwise specified, (age range – 45 –to 78 years) 6 were well differentiated and 2 were moderately differentiated. All patients had pain abdomen. Other presenting complaints were vomiting (4/10), jaundice (2/10), fever (2/10) and abdominal distension (1/10). Sites of metastasis noted were liver (4 cases), three of which also had lymph node involvement. One case had isolated lymph node metastatsis at presentation. Lymph nodes involved were abdominal nodes including periportal, para aortic and coeliac nodes. Radiologically, gall bladder wall thickening and mass lesion was seen in 3 cases each. Other 4 cases revealed cholelithiasis and sludge. Grossly, polypoidal growths measuring 2x6cm in diameter or flat lesions with thickening of the wall were noted. Adjacent mucosa showed gastric metaplasia in 7 cases, of which 2 also had intestinal metaplasia, 5 cases had mild and one severe dysplasia. All patients were given systemic chemotherapy.

Patient with signet cell adenocarcinoma presented with pain abdomen and loss of appetite. Radiology revealed polypoidal lesion and thickened wall along with metastasis to omentum and lymph nodes. Patients with signet cell adenocarcinoma and adenosquamous adenocarcinoma (Figure 3) refused treatment and were lost to follow up.

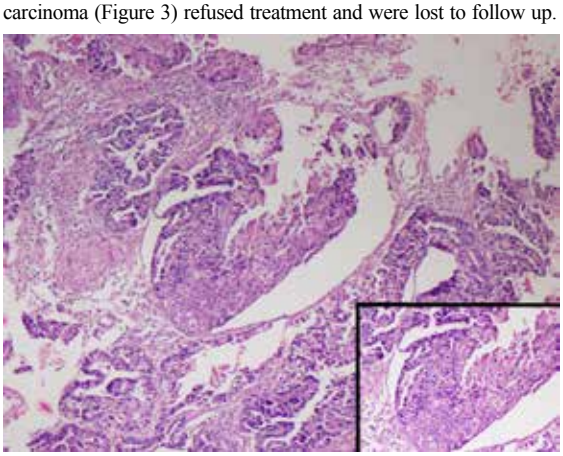

Figure 3: Photomicrograph showing adenosquamous carci-

noma ((H&E X4x) Inset ((H&E X10x)

DISCUSSION:

Epithelial neoplasms of the gall bladder are uncommon with varied pathogenesis. Gall bladder carcinoma is the most common malignancy of the biliary tract and accounts for 3% of all tumours. Majority of these patients are diagnosed at an advanced stage associated with grim prognosis. Early detection of high risk patients and prophylactic treatment by simple cholecystectomy has excellent clinical outcome. (4)

Gall bladder cancers show female predominance affecting individuals in sixth and seventh decade. (5) No specific gender predilection was seen, however, similar age profile was present in our study.

Major risk factors of gall bladder cancers include gall stones and chronic cholecystitis. Gallstone is an important etiology in development of gall bladder carcinoma but the causal relationship is not proven. Chronic irritation and inflammation may lead to epithelial changes such as ulceration, metaplasia and dysplasia. The presence of gallstone and features of chronic cholecystitis in majority of patients with adenomas, dysplasias and gall bladder carcinoma in the present study supports this relation. Martinez et al have shown increased frequency of dysplasias, adenomas, carcinoma in situ and invasive carcinoma in the presence of cholelithiasis. A high prevalence of gall stones in gall bladders with metaplastic, dysplastic and neoplastic changes than those gall bladders which showed no epithelial changes were also seen. (6) Choledochal cysts, anomalous pancreaticobiliary duct junctions and polyps are other risk factors. (4)

The biological significance of premalignant conditions in the gallbladder such as adenomas and dysplasias has not been completely understood. Two models for their malignant transformation have been proposed: the dysplasia–carcinoma sequence and the adenoma–carcinoma sequence. (3) Morphologically, the dysplasia–carcinoma sequence is most pausible. Infrequent presence of adenoma in the mucosa near invasive cancers makes the possibility of adenoma-carcinoma sequence remote. The histological spectrum from dysplasia to the carcinomas in situ, associated with invasive gallbladder carcinoma, is a frequent finding in the mucosa adjacent to the tumors and favours carcinogenetic model. (6) Dysplasias, in turn, are thought to arise in mucosa showing metaplasia,however, the exact relation is unclear. Microsatellite instability, Loss of heterozygosity and the inactivation of genes like p53, CDH1and p16 have been demonstrated with greater frequency in the areas of metaplasia in the mucosa associated with cancer. (7) The time period required for disease to progress from dysplasia to carcinoma has been estimated as 10 to 15 years in various studies. (8,9) This emphasizes the importance of large time frame available for prophylactic cholecystectomy . In the present study, of the 12 cases of gall bladder cancers, metaplasia was seen in 7 and dysplasia in 6 cases. None of them had adenomas. This suggests a definite close association between metaplasia, dysplasia and carcinoma favoring the dyplasia-carcinoma sequence. Albores Saavedra et al 2011(10) and Dowling & Kelly 1986 (11) showed that metaplastic changes were seen in 11 out of 14 cases of gall bladder carcinoma. Intestinal metaplasia was seen more frequently than gastric metaplasia.(6) In contrast, gastric metaplasia was more frequent in our study.

Gall bladder neoplasia is difficult to detect clinically and radiologically. Clinically, they present with signs and symptoms of acute or chronic cholecystitis. On ultrasonography (USG) , solid intraluminal mass is seen in only few cases while most show diffuse wall thickening which may suggest a chronic inflammatory condition. (1,8,12) In the present study, 2 of 5 cases of adenoma, all cases of dysplasias and 6 of 12 cases of cancers were diagnosed clinico- radiologically as cholecystitis. Fortunately, most of the incidentally detected carcinoma are surgically resectable, with a good survival rate. (4,12) In the present study, 6/12 cases had metastasis on presentation.

On gross examination of cholecystectomy specimen, no obvious lesion, diffuse thickening, nodule or polyp may be detected.(2) Careful examination and sectioning of all cholecystectomy specimens is essential to detect these epithelial abnormalities.

Histopathological spectrum of gall bladder neoplasia includes adenoma, dysplasia and invasive carcinoma. Adenomas are sessile or pedunculated tumours classidied as tubular, papillary and tubulopapillary. Pyloric gland metaplasia is very common in adenomas as seen in our series. (11) Dysplasias of the gall bladder mucosa is often found coexisting with invasive cancers. They are further graded as mild, moderate and severe based on the degree of atypia. Commonly, adjacent mucosa exhibits gastric or intestinal metaplasia. (11) In the present study, 3 of the 7 cases showed metaplasia. Among the invasive neoplasms, adenocarcinomas are the most frequent histological subtype accounting for 90-95% of all cases. Other subtypes like squamous cell and adenosquamous carcinomas are rare. (11)

CONCLUSION:

Absence of clinico-radiological suspicion and increasing frequency of incidentally detected epithelial neoplasms in routine cholecystectomy specimen, emphasizes the importance of a careful histopathological examination of all cholecystectomy specimens. Histopathological features support the relationship between gallstones, dysplasia and carcinoma of the gall bladder warranting a vigilant microscopic examination and encouraging prophylactic cholecystectomy in high risk patients.

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