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FREQUENCY OF GALL BLADDER CARCINOMA ON ROUTINE HISTOPATHOLOGY AFTER CHOLECYSTECTOMY

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ABSTRACT

A retrospective study was conducted to find the incidence of carcinoma of gall bladder. Data were collected from the patients admitted with cholelithiasis in surgical units of different hospitals of Karachi during the year July 2002 to June 2004. All of them underwent Cholecystectomies. Out of 153 patients, 62 (40.5 %) were male and 91 (59.5 %) were females with mean age of 40 and 54 years respectively.

The patients were admitted with commonest clinical presentation of upper abdominal pain, dyspepsia and palpable gall bladder. Liver function tests were altered in most of the cases (72.5 %). Ultrasonography was carried out on all patients. Results showed cholelithiasis in 87.6 % cases, wall thickening 90.2 %, wall irregularity 32.7 % and CBD dilatation in 39.2 % with and without stones. Histopathology of most of the above cases revealed inflammatory changes and patients were diagnosed with adenocarcinoma of gall bladder. Follow up was not possible due to lack of coordination between surgical unit and pathology department.

The incidence of neoplasia on routine histopathology after cholecystectomy for cholelithiasis was found to be as 8.5 %.

Key words: Gall bladder, adenocarcinoma, and cholelithiasis.

INTRODUCTION

Gall bladder carcinoma was first described in 1777 (Nevin, 1976). It is the 5th commonest malignancy of gastrointestinal tract and is slightly more common in females, occurring most frequently in 7th decade (Kyria, 1999; Cotran *et al*., 1999). The peak age is between 65 to 69 years (Jose and Jurge, 1996). The highest mortality rate has been reported in Chilean mapuches Indian, Hispanic Americans and American Indians. Most cases originate in the fundus 60%, body 30%, and in the neck 10% (Cotran *et al*., 1999). Presenting symptoms are insidious and typically indistinguishable from those associated with cholelithiasis, abdominal pain, jaundice, anorexia, nausea, and vomiting. The fortunate patient will develop palpable gall bladder and acute cholecystitis, before extension to adjacent structures. The disease is either discovered accidentally during cholecystectomy or proceeds with nonspecific symptoms or inflammatory mass in right hypochondria. The nonspecific symptoms include anorexia, nausea, vomiting, and weight loss (Cuschieri and Bouchier, 1998).

Many epidemiological studies have suggested genetic susceptibility for carcinoma gall bladder among American Indians, the familial aggregates has been reported in USA and other countries. The gall bladder containing stones or infective agents develops carcinoma as a result of irritative trauma and chronic inflammation. Carcinogenic derivatives of bile acid may also play a significant role.

Chronic inflammation by *Salmonella typhi* has also been associated with an increased risk of gall bladder carcinoma (Caygill *et al*., 1994; Caygill *et al*., 1995). The association of carcinoma gall bladder with stones has been known for over 100 years. Gallstones are risk factors for developing gall bladder carcinoma (Gutafsson *et al*., 2001). Gallstones are present in 60-80% of cases. In Asia pyogenic and parasitic diseases of biliary tree is common. *Opisthochis viverrini. Opisthochis sinensis* infection has been associated with intra hepatic and extra hepatic bile duct. The parasitic cause includes a chronic inflammatory reaction with considerable epithelial proliferation of the bile duct followed by metaplastic proliferation. Patients of ulcerative colitis and primary sclerosing cholangitis often develop carcinoma of extra hepatic bile duct (Jose and Jurge, 1996). The histological classification of tumor of gall bladder and extra hepatic bile duct is proposed by WHO based primarily on morphological characteristics and ranges from epithelial tumors, non epithelial mesenchymal tumors, lymphomas, unclassified, and tumor like conditions. More than 50 entities have been classified in this classification. (Jose and Jurge, 1996).

Approximately 10-15% of invasive gall bladder carcinomas were recognized on gross examination. The clinical presentation of carcinoma gall bladder is frequently discovered late, which accounts for the poor prognosis (Kyria, 1999) Radiological investigation (ultrasonography and CT scan) plays a vital role in the diagnosis of suspected cases (Kumar *et al*., 2000). Ultrasonography identifies the advanced disease but misses the early curable lesion of mass in gall bladder.

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Sonography is highly accurate for detecting a mass lesion, gall stones, metastasis, and ascites. Its sensitivity is poor for staging nodal spread (Pandy *et al*., 2000). Patients with *in situ* carcinoma gall bladder are curable by chemotherapy and for patients with carcinoma limited to gall bladder will have 5 years survival rate of 32%. Patients with known liver metastasis, distant metastasis, or distant extension to adjacent organs die soon after the diagnosis (Jose and Jurge, 1996).

PATIENTS AND METHODS

The patients having cholecystitis and cholelithiasis were selected without clinical suspicion of malignancy for further investigation of the disease. The patients admitted to the surgical department through out-patient department in different hospitals of Karachi, 153 were selected for the present study, out of which 62 were males with mean age of 40 ± 5 years, and 91 were females with a mean age of 54 ± 5 years. All patients had their liver function test (LFTs) and ultrasonography of whole abdomen was done beside other baseline investigations found to be altered. Open cholecystectomy was done in all patients. The gall bladder specimens were fixed in 10% formalin and embedded in paraffin. 5 micron thick sections were made by ERMA microtome machine (Japan). Routine hematoxylin and eosin (H&E) staining was done, special stain PAS was also performed in the cases diagnosed as adenocarcinoma to confirm the further diagnosis and origin of the tumor.

RESULTS

The study was conducted during the year July 2002 to June 2004. A total of 153 patients (62 males and 91 females) were included in the present study. The mean age was 54 ± 9 yrs. The presentation of patients shown in table 1. Among 153 patient, 107 (69.9%) were presents with the symptom of upper abdominal pain, 127 (83%) told about dyspepsia and in 134 (87.6%) the gall bladder was palpable. The liver function test and ultrasonography was also done for all patients before doing cholecystectomy. The liver function was altered in 72.5% of patients and ultrasound study reveals cholelithiasis in 87.6% of cases (Table 2). After cholecystectomy the histology shows acute cholecystitis (21.6%), chronic cholecystitis (69.9%) and adenocarcinoma in (8.5%) of cases (Fig. **1**). The incidence of neoplasia on routine histopathology after cholecystectomy for cholelithiasis was found to be as 8.5 %.

Table1. Baseline characteristics of patients.

	No of Cases (%)
Total No. of Patients	153
Males	62 (40.5)
Female	91 (59.5)
Age (Years)	
Mean	54 ± 9
Upper Abdominal Pain	
Absent	46 (30.1)
Present	107 (69.9)
Dyspepsia	
Absent	26 (17.0)
Present	127 (83.0)
Palpable Gall Bladder	
No	19 (12.4)
Yes	134 (87.6)

Table 2. Biochemical and Ultrasonograhic findings of Patients.

	No of Cases (%)
Liver Function Test	
Normal	42 (27.5)
Altered	111 (72.5)
Ultrasound Findings	
Cholelithiasis	134 (87.6)
Wall Thickening	138 (90.2)
Wall Irregularity	31 (32.7)
CBD Dilatation	60 (39.2)
Histological Findings	
Acute Cholecystitis	33 (21.6)
Chronic Cholecystitis	107 (69.9)
Adenocarcinoma	13 (8.5)

CBD = Common Bile Duct

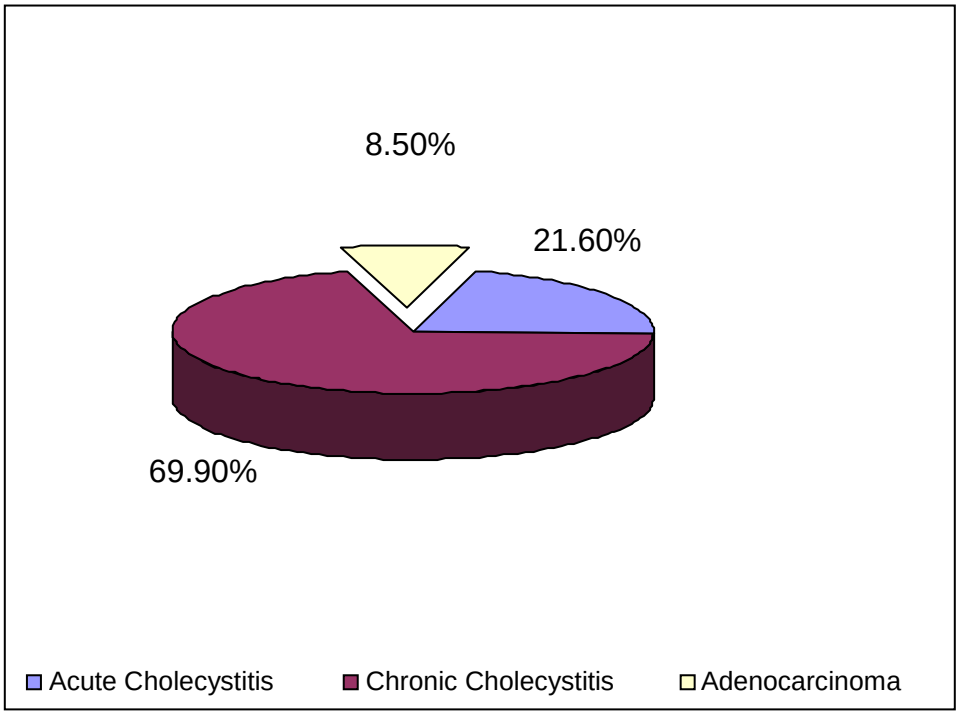

Fig. 1. Showing histological distribution of cases.

DISCUSSION

Carcinoma of gall bladder though being the most common malignancy of the biliary tract, it is often diagnosed at advanced stage as early as patients suffering from advanced disease symptoms. In its early stage its clinical presentation is non-specific and discovered accidentally during routine cholecystectomy for cholelithiasis and on histopathology of cholecystecomty specimens. It has been established that dysplasia and carcinoma in site precede mostly gall bladder carcinomas. Relatively little is known about the natural history of these precursor lesions. Most dysplasia and carcinoma in situ diagnosed after cholecystectomy when the entire lesion is removed (Albores *et al*., 1992).

Two most important features are having the greatest effect are pathologic stage of the disease and histological grade of the tumors. For patients with neoplasm limited to wall of the organ the survival rate is 32%, and with the known liver metastasis of direct extension to adjacent organs die soon after diagnosis (Jose and Jurge, 1996).

The demographic profile, pathology and survival of patients with gall bladder cancer, extra hepatic bile duct cancer and ampullary carcinoma are similar in New Zealand to that of other Western countries. However, New Zealand Maori have a relatively high incidence of gall bladder cancer and the incidence is equal in both Maori men and women (Koea *et al*., 2002).

In our observations the gall stones were found in 87.6 % of patients. It is postulated that gall bladder carcinoma may be intimately associated with large or numerous cholesterol gallstones that in the first instance may interfere with the mechanical functioning of the gall bladder. The size as well as the number of gallstones present in the gall bladder may contribute significantly to the promotion of a gallstone filling defect of the gall bladder that may cause chronic mechanical damage to the gall bladder mucosa. The studies support the hypothesis that gall bladder carcinoma is an age-dependent malignancy, present mostly in women that may be intimately associated with long-standing gallstone disease of the gall bladder (Vitetta *et al*., 2000). Patients with gallbladder carcinoma had significantly larger stones, regardless of the number of stones present ($P < 0.001$). We postulate that the increase in the number and size of the stones among patients with gallbladder carcinoma could simply be an effect of aging or it could be a reflection of the long-term presence of stones in the gallbladder rather than some particular chemical or physical influence (Csendes *et al*., 2000).

The distribution of out come of cholecystectomy in our data showed that among 153 patients 33 (21.6 %) has acute cholecystitis, 107 (69.9 %) with chronic cholecystitis while 13 (8.5 %) has adenocarcinoma. In acute cholecystitis the pathological findings were in accordance with clinical feature in only 46.2% but in chronic or subsided cholecystitis pathology confirmed in 97.5%. Carcinoma of the gallbladder was found in 0.9 per cent.

Multiple gallstones were found in 67.3%, single stone in 23.5%, sand stones in 2.1% and acalculous cholecystitis in 7.1%. Combined gallstones and CBD stones were found in 9.8 % (Chunhamaneewat and Punyagupta, 1999).

Carcinoma of the gallbladder is diagnosed in 0.3-1.5% of all cholecystectomy specimens. The overall incidence of unsuspected gallbladder carcinoma in our series was 0.35% (Weinstein *et al*., 2002). Incidental carcinoma of the gallbladder can be found histologically in 1-2% of specimens after surgery of benign diseases of the hepatobiliary tract (Hohaus *et al*., 1997).

The incidence of gall bladder carcinoma in our study is 8.5 %, which accords with most of the studies in out part of the world. The incidence of gall bladder cancer is variable all over the world and range from 3-28 % as reported by various researchers. The tumors were usually considered radio resistant but now a recent study has proved that there is a slight improvement of survival after adjuvant or palliative radiotherapy especially in the advanced stage of the disease. To conclude, gall bladder carcinoma is characterized by late diagnosis, ineffective treatment and poor prognosis. There is a need for early diagnosis and further research at the cellular and molecular level.

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