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INCIDENTAL GALLBLADDER CARCINOMA IN PATIENTS UNDERGOING CHOLECYSTECTOMY FOR CHOLELITHIASIS; A CLINICOPATHOLOGICAL STUDY

Kolesistektomi yapılan hastalarda insidental safrakesesi karsinomu; Klinikopatolojik bir değerlendirme

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ABSTRACT

Gallbladder carcinoma is the most common carcinoma of the biliary tract. Although it is a relatively rare disease, it is a highly aggressive malignancy. The prevalence of carcinoma in the gallbladder is greatly variable in different parts of the world. Gallbladder carcinoma is diagnosed pathologically in 0.3-1.5% of cholecystectomy specimens. Among the 500 cholecystectomy specimens 9 cases were diagnosed to be a case of malignant disease (1.8%). Rest of the cases (491, 98.2%) was benign in nature with different type of conditions. Furthermore, of all carcinoma gallbladder cases 75-90% occur in the setting of cholelithiasis and the epidemiology of gallstone parallels that of gallbladder carcinoma.

Key words: Cholecystectomy, cholelithiasis, carcinoma, incidence.

ÖZET

Safra yollarında en fazla görülen tümör safrakesesi kanserleridir. Nadir görülmekle beraber oldukça agressif bir tümördür. Görülme sıklığı dünyanın değişik yerlerinde farklılıklar göstermektedir. Kolesistektomi spesmenlerinde %0.3-1.5 sıklıkta kanser görülmektedir. 500 kolesistektomi spesmenimizin 9'unda (%1.8) safrakesesi kanseri saptadık. Kalanlarda (491, %98.2) ise benign patolojiler saptandı. Bununla birlikte safrakesesi kanseri olan vakaların %75-90'ında kolelithiazis ile birlikte olduğu bilinmektedir.

Anahtar kelimeler: Kolesistektomi, safra kesesi taşı, karsinom, görülme sıklığı.

INTRODUCTION

Gallbladder (GB) carcinoma is the 5th most common malignancy of the G.I. tract and traditionally has been considered an incurable disease with an extremely poor prognosis. It was first described in 1771 by de Stoll of Vienna, who recorded the necropsy finding in 3 patients (1). Almost 240 years later, late diagnosis and absence of effective treatment for many patients remains typical feature of this disease (2). Demographically women are three times more vulnerable to develop GB malignancy than men across all populations that have been studied (3,4). It is usually a disease of is commonly cited risk factor for the development of gallbladder carcinoma is gall stones, particularly large stones and cholesterol stones.75%-90% of gallbladder malignancy occurs in the setting of cholelithiasis (5-8). The epidemiology of cholelithiasis parallels that of gallbladder cancer; however, confounding issues confuse whether this is truly a cause and effect relationship. Chronic inflammatory conditions of the gallbladder, such as cholecystoenteric fistula and chronic infection with typhoid bacillus also have been associated with a risk of gallbladder carcinoma. The presence of an anomalous pancreaticobilliary junction with a long common channel also have been implicated in risk of gallbladder carcinoma and it also

may be related to chronic inflammation (7). Most of the carcinomas of gallbladder are adenocarcinomas, some are papillary and others are poorly differentiated to well differentiated infiltrating tumours, 5% are squamous cell carcinomas or have adenosquamous differentiation, a minority are carcinoid tumors. Clinical presentation of gallbladder malignancy and benign gallbladder disease is almost similar and most of the times it is masked by chronic cholecystitis. Preoperative diagnosis of carcinoma of gallbladder is the exception rather than the rule, occurring in fewer than 20.0% of patients. Hence, It is likely for finding gallbladder tumours incidentally during surgery done for stones or biliary tract diseases. Incidental carcinoma of gallbladder includes incidental finding of carcinoma in histopathological examination of gallbladder specimen sent after cholecystectomy performed for benign gallbladder disease or removed during other abdominal surgeries. Gallbladder carcinoma is diagnosed pathologically in 0.3-1.5% of cholecystectomy specimens. The prognosis of patients in whom it is diagnosed preoperatively is very poor as many of them are unresectable at presentation. In 15-30% cases there is no evidence of malignancy before or during the operation and the disease is identified microscopically post operatively. Theoretically, this group carries the best prognosis (8). Incidentally diagnosed gallbladder malignancies in cholecystectomy specimens are mostly confined to the muscular coat (T1tumors) or invading into subserosal layer (T2 tumors), because they are not obvious in imaging studies. T1 tumors do not penetrate through the muscular layer and because a simple cholecystectomy dissects the perimuscular layer, this operation is sufficient theoretically. It is crucial to achieve a negative margin and the cystic duct margin should be reviewed to ensure this. Overall, the cure rate varies from 85% to 100% in different studies with a simple cholecystectomy. Simple cholecystectomy is the appropriate treatment particularly for T1a tumors, and extended cholecystectomy may be required for T1b tumors on a case to case basis. Cholecystectomy for incidentally found T2 tumors is noncurative and re-resection is justified in the form of resection of liver and portal lymphnodes (9). In this observational study it is aimed to determine the rate of incidental gallbladder carcinoma in our setting. During the study period the specimen of gallbladder obtained after open or laparoscopic cholecystectomy has been examined to determine the histopathology of the gallbladder and the data obtained are compared with that of the published literature. The author has also tried to detect common characteristics in this particular group of patients.

MATERIAL AND METHOD

Patients attending surgical out patient department at Calcutta National Medical College Hospital with symptomatic gall stone disease were clinically evaluated and investigated and all the data were recorded in a suitable proforma. Patients were admitted and after check up for anaesthetic fitness was done, they underwent cholecystectomy either laparoscopically or through open approach. Peroperatively each gallbladder specimen was cut open to look for any suspicious features. Each specimen was send for histopathlogy examination and the results were reviewed. All patients undergoing cholecystectomy due to cholelithiasis are included in the study. The patients who eventually diagnosed as gallbladder carcinoma or have suspicion of carcinoma gallbladder pre-operatively are excluded from the study. The main objective of the study is to find out the incidence of incidental gallbladder carcinoma and to review the risk factors associated with it. Hence, no control group has been taken and no statistical method has been applied for comparison with other studies.

RESULTS

Among the 500 patients presented with cholelithiasis, 115 were male (23%) and 385 were female (77%). Most of the patients presented with pain in right hypochondrium associated with nausea and vomiting. Gallbladder was palpable in 15% of patients and 8% of patients presented with some amount of jaundice. All the patients included in the study primarily had cholelithiasis. Majority of them had multiple calculi in the gall bladder lumen (68%) and in 32% of cases it was a single stone. During sonography GB was distended in 57% cases mostly due to physiological distension, some cases were due to single stone impacted at the neck. Acute cholecystitis patients revealed distended gallbladder with thickened and oedematous wall with pericholecystic fluid collection in some cases. In 23% cases gall bladder was contracted owing to chronic cholecystitis. Overall in 28% cases gall bladder wall was found to be thickened, mostly diffuse homogenous in acute conditions. But in some cases thickening was irregular and mucosal thickening was localized in neck, fundus. Associated choledocholithiasis was found in 13% cases with variable amount of CBD dilatation. In additional 4% cases dilated CBD was present without any intraluminal stones.

Once diagnosis was made other routine laboratory and radiological examination was done and after preanaesthetic checkup patients were operated for cholecystectomy either laparoscopically or open approach. In this study 275 patients undergone laparoscopic cholecystectomy and 210 patients were operated through open approach. In case of 15 patients laparoscopic approach was converted to open approach due to technical difficulties. All the operations were done in elective setting. Per operatively 48 patients were found to have abnormally thickened gall bladder wall with some irregularity in mucosa. These specimens were marked with sutures and weresend for histopathological examination along with other normal gall bladder specimens.

Among the 500 cholecystectomy specimens 9 cases were diagnosed to be a case of malignant disease

(1.8%). Rest of the cases (491, 98.2%) was benign in nature with different type of conditions (Table 1). Benign conditions of gallbladder were mostly chronic cholecystitis frequently associated with ulceration of mucosa, prominent Rokitansy-Aschoff's (RA) sinus, cholesterosis and adenomyosis. In some cases chronic cholecystitis with areas of antral metaplasia were noted. Others in minority included chronic cholecystitis with acute exacerbation, follicular cholecystitis, eosinophilic cholecystitis, xanthogranulomatous cholecystitis, empyema gangrenous cholecystitis, tuberculosis, acute cholecystitis.

Table 1: Clinical data of incidental gallbladder carcinomas.

Age / Sex	Clinical Features	Ultasound Findings	Preoperative Diagnosis	Peroperative Findings	Histopathology Report
38/F	Chronic pain, vomiting	Contracted GB, single stone 25 mm in dm	Chronic cholecystitis	LC-Thick fibrous wall	Invasive adenocarcinoma well differentiated (PT1b)
67/M	Pain,vomitting dyspepsia	Multiple stones Thick oedematous wall	Acute cholecystitis	OC-No suspicious lesion	Acute on chronic cholecystitis with focal carcinoma in situ (Tis)
55/F	PalpableGBpain, anorexia	Hugely distended GB Multiple small calculi Neck obscured by sludge & Thickened mucosa	Chronic cholecyctitis	OC-Thick irregular mucosa in the neck, enlarged cystic node	Infiltrating mod.differentiatedadenoCA invasion upto serosa (PT2)
62/F	Pain, mild jaundice	Single stone in GB, dilated CHD with single stone near the cystic duct. GB wall thickened (5 mm)	Chronic cholecystitis with choledocholithiasis	OC-Mirizzi syndrome, no stone in CBD, thickened mucosa of GB	Intramucosal well differentiated carcinoma with focal area of muscle invasion (PT1b)
76/F	Pain, dyspepsia	Single large stone 22 mm, distended GB with wall thickness 4 mm	Chronic cholecystitis	OC-No suspicious lesion	Well differentiated adeno carcinoma confined to mucosa (PT1a)
60/M	Acute pain, vomiting	Distended GB, oedematous thickened wall 5 mm, multiple calculi	Acute cholecystitis	LC-No suspicious lesion	Well-mod differentiated intramucosal adenocarcinoma (PT1a)
63/F	Pain anorexia, fever, palpable GB	Hugely distended GB with impacted stone in the neck 21 mm wall thickness 5 mm	Empyema GB	OC-Irregular mucosa	Poorly differentiated adeno carcinoma infiltrating subserosa (PT2)
52/F	Chronic pain dyspepsia	multiple stones with one large stone 24 mm	Chronic cholecystitis	OC-Large stone impacted in the fundus with mucosal ulceration	Well differentiated adenocarcinoma invading the muscle layer (PT1b)
55/F	Epigastric pain	Contracted GB with single large stone 17 mm	Chronic cholecystitis	LC-No suspicious lesion	Carcinoma in situ

Out of 500 cholecystectomy patients 9 patients were incidentally diagnosed as gall bladder malignancy in histopathological examination. Out of 9 patients 2 were male and 7 were female (M: F-1:3.5). Minimum age of presentation was 38Yrs and maximum age of presentation was 76yrs with mean age of presentation was 59.7 yrs (Figure 1).

Clinically no patients had any suspicion of malignancy. Most of the patients presented with pain right hypochondrium along with nonspecific symptoms like nausea, vomiting, dyspepsia, epigastric pain. Gallbladder was palpable in two patients due to impacted stone at the neck and one patient presented with obstructive jaundice due to mirizzi syndrome. Preoperatively clinical diagnosis of chronic cholecystitis was made in 6 out of 9 patients (i.e. 60% cases). Two patients had features mimicking acute cholecystitis. Ultrasonography revealed single large stone in 5 patients (i.e 55.5% cases). Average diameter of the stones was 21.8 mm. In case of 4 patients (45%) ultrasound predicted thick wall (>4 mm) and irregular mucosa but no suspicion of malignancy was aroused. Among the carcinoma patients 3 underwent laparoscopic cholecystectomy and 6 patients were subjected to open cholecystectomy. On macroscopic examination no abnormality was noted in four cases (45%) but in other cases there were some forms of abnormality like thick and irregular mucosa, mucosal ulceration which ultimately proved to be cases of gallbladder cancer. All the malignancies which were diagnosed incidentally were early GB malignancies. Two cases were in situ carcinoma, rest of the cases were all adenocarcinoma variety. Two patients were stage T2 cancer, rests were either T1a or T1b cancer.

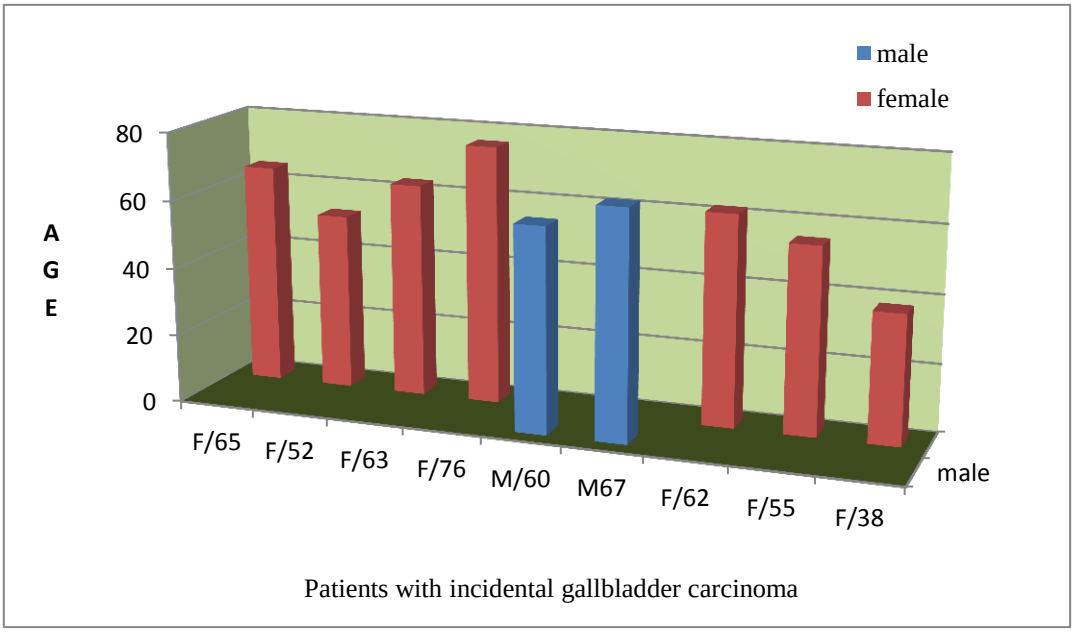

Figure 1: Diagram shows the frequency distribution of age & sex of incidental gallbladder cancer patients.

DISCUSSION

Total 500 patients with cholelithiasis operated for cholecystectomy were studied during January 2011 to April 2012 period. The age of patients with gallbladder disease ranged from 14 yrs to 78 yrs and were most commonly found in the 5th decade (139/500 cases, 27.8%). There were 115 males and 385 females with M:F ratio of 1:3.34. Out of 500 cases, 491 were benign gallbladder disease and 9 were neoplastic lesions of gallbladder on histopathological examination. The age of patients with malignancy varied from 38yrs to 76yrs with highest peak in the 6th decade. Mean age for malignancy was 59.7 yrs. Malignancy was also more frequently encountered in females (7/9, 77.8%). Among the benign conditions detected in histopathological examination chronic cholecystitis was most commonly encountered (67% cases). Chronic cholecystitis was frequently associated with mucosal ulceration and Rakitanski Aschoff's sinus followed by cholesterosis and antral metaplasia. Mittal et al (36) had similar findings; they found 77% cases of chronic cholecystitis. Other than chronic cholecystitis routine histopathological examination found significant case of acute exacerbation of chronic cholecystitis (18.4% cases), acute cholecystitis, (8% cases) xanthogranulomatous cholecystitis (2.6% cases) in this study.

Out of the 9 cases of incidentally diagnosed gallbladder malignancy 2 cases were in situ adenocarcinoma and rests were invasive adenocarcinoma. Silk et al (32) and Ataur et al (28) found 100% cases of adenocarcinoma in their studies. Gallbladder malignancy is a rare entity, however, is common in the gastrointestinal tract and particularly observed in women from Chile, Japan, Northern India and Pakistan. The etiology of this malignancy is complex but there

is strong association with gallstones. Most are diagnosed at advanced stage with dismal prognosis having 5 years survival rate of less than 5.0%. Detection at early stage has excellent prognosis increasing up to 90.0-100.0% 5 years survival rate (27). However, early detection is not possible due to delayed onset of symptoms or is masked off by chronic cholecystitis and is usually detected after simple cholecystectomy as incidental finding.

In this study the incidence rate of incidental GB carcinoma in routine post-cholecystectomy cases was 1.8%. Amanullah et al (1.8%) and Shrestha et al (1.4%) have found the incidence similar to ours whereas Khoo JJ &Nurul reports rate of incidental carcinoma to be 0.62% .Tantia et al, Mittal et al studied incidental gallbladder cancer in India and their rate of incidence were 0.6%, 0.99%, respectively. Daphna et al observed 0.3% incidence, Zhang WJ et al has shown its occurrence as low as 0.19%. It was even higher as shown by Shigeki et al, finding incidence of incidental gall bladder cancer to be 4.7% and Navqi et al has found its occurrence as high as 5.9% (18-26, 36)

The variety in the incidence may be due to inadequate preoperative evaluation or less number of cholecystectomy used for the study purpose. This is because the incidence of primary carcinoma of the gall bladder is itself low and hence finding of incidental carcinoma would be low too. Different incidence rates may also be attributed to different ethnic group, race and religion. Incidentally diagnosed gallbladder cancers were commonly seen in 6 th decade of life with mean age at presentation being 59.7 yrs and more commonly encountered in female (77.8%). Similar findings were encountered in studies by Ataur (28), Hsieh (29), Tantia and their co-workers. The higher incidence of overall gallbladder disease in females (three times more in this study) explains the more frequent occurrence of GB malignancy in them. In contrast to benign diseases, malignancies were found to increase with increasing age. Chronic irritation and inflammation of the gallbladder, which leads to mucosal dysplasia and subsequent carcinoma that takes a long duration for promotion of tumor proliferation and hence the occurrence of malignancy in the elderly age group. There is a regional variation in male to female ratio from 1:1.1 to 1:5.5 in the world literature. As evident from the previous table. Female to male ratio is even high in those areas where the gallbladder disease and gallbladder carcinoma is rare. Only Smithies has presented a small series of carcinoma gallbladder which is more common in males than females (30) .In our series 77.8% were females and 22.2% were males with male to female ratio of 1:3.3 which is similar to regional and international studies. Gallbladder malignancy doesn't have a typical clinical feature and its usual presentation mimics that of benign gallbladder disease. Most of these patients presents with syndromes of acute or chronic cholecystitis (10,31) Skil et al (32) reported that there were no identifiable symptoms of carcinoma gallbladder and duration of symptoms are variable in different patients. Pain is the most prevalent symptom (50%) as described by Wanebo (11). In this study symptoms in majority of patients were pain, nausea, and vomiting and 6 patients were diagnosed preoperatively as chronic cholecystitis and 2 patients were as acute cholecystitis. Preoperative ultrasonography predicted thickened wall (>4 mm) in 6 out of 9 cases of incidental gallbladder cancer and in 2 cases out of those 6 cases thickened wall were attributed to acute oedematous condition of gallbladder. So actually out of 9 cases only in 4 cases (45%) ultrasound predicted thickened wall. Agarwal & Kapoor said in their literature that an irregular or localized thickening of the GB wall should be treated as 'suspected' gallbladder cancer and extended cholecystectomy should be done in those cases (17). In those 9 cases of incidentally diagnosed gallbladder cancer, 5 patients (55.5% cases) had single large calculi and average diameter of the stones was 21.8 mm. It is a well-established fact that gall stone size is related to the risk of developing malignancy. Diehl first studied the relation of gallstone size and risk of gall bladder cancer in 1983 and suggested that The larger the gall stones (>2-3 cm in dm), the greater the association with gall bladder carcinoma (13). Different studies also support this fact (14-16). It is a standard practice to perform routine histopathological examinations for all cholecystectomy specimens. Various studies including the working report of Royal College of Pathologists have recommended for that every gallbladder specimen should be examined, as significant pathology may be present with normal gross morphology (33). Samad and Amanullah and also Shreshtha et al shared the same strategy (21,24). Recently few other investigators have challenged this practice. They have suggested that all cases of GB carcinoma have some macroscopic features like thickened fibrotic wall, mucosal ulceration, nodular mucosa or polyploidy projections which can be used as a guide for sending for histopathology. Bazoua et al observed that all gallbladder cancers had thickened fibrotic wall (34). Different studies also showed similar observation that, abnormal macroscopic appearance were present either pre or intraoperatively in all cases of invasive carcinoma and thus recommended for selective policy rather than routine histological examination of non fibrotic or thickened-wall gallbladder (35-38). This study showed that radiological and peroperative findings were not helpful in raising high index of suspicion in all the cases of incidental carcinomas. Preoperative diagnosis of malignancy was difficult and combined preoperative and intraoperative findings failed to detect 55.0% of malignant cases in this study. Macroscopic findings of all incidental carcinomas had thick wall gallbladder in those studies where selective histolopathology examinations were recommended. However, this study showed thickened GB mucosa in only 5 cases of incidental carcinomas and the remaining 4 had no suspicious lesion or any specific chan-

ges intraoperatively. While on gross, other than thickened GB, nonspecific mucosal changes such as, irregular, granular mucosa, mucosal ulceration, contracted GB were noted. Therefore no specific clinical or macroscopic finding can be assigned to characterize incidental carcinoma pre or intraoperatively to have clinical suspicion of malignancy. Only histological examination remains the tool for the detection of occult malignancy. Authors who propose for selective policy of histological examination state that incidental carcinomas if found during histopathological examination would be at early stage and simple cholecystectomy performed for benign gallbladder disease would be sufficient enough in giving good clinical outcome (34-38). In contrast to this statement, this study reveals not only early stage (T1a and T1b) incidental carcinomas but also, 2 cases at stage T2. In incidental carcinoma of gallbladder at stage T2, second radical operation is suggested by Steinert et al (40). Even for the management of early stage carcinoma, especially T1b, Vincenzo et al (39) suggested more aggressive surgery, as there was improvement of survival rate in comparison to those treated with simple choecystectomy. Similar view is shared by Mishra et al (12) recommending re-resection for all disease except Stage IA, for patients whose cancer is an incidental finding on pathologic review. However, there is still a controversy regarding management of GB malignancy at stage T1b. Decision upon further surgical management of the incidental carcinomas thus depends upon the stage after pathological examination as well as, patient's fitness for re- surgery. Routine histological examination of all gallbladder specimen is therefore well justified as finding of incidental carcinoma might alter the management and thus the clinical outcome.

In conclusion; the rate of incidental gallbladder carcinoma in this study was 1.8%. Gallbladder carcinoma occurs mostly in females in 6th decade of life. In this study male female ratio of gallbladder carcinomas was 1:3.5 and mean age was 59.7yrs. Gallbladder malignancy occurs in the setting of cholelithiasis. In this study 55.5% patients had single large stone with average diameter more than 20mm. Most of the gallbladder carcinomasare missed during preoperative, ultrasound and intraoperative examination. Macroscopic abnormal findings simply cannot be relied on selecting gallbladder specimen for suspicionof malignancy, and even nonspecific macroscopic changes or intraoperatively normal looking gallbladder to surgeon's eye might harbor malignancy. For every incidentally found carcinoma, simple cholecystectomy may not be sufficient as some might be detected at locally advanced stage or at T1b requiring further aggressive surgery. Keeping in view of all these possibilities, it is recommended that routine histological examination of every cholecystectomy specimen should be done regardless of macroscopic appearance of gallbladder. This study also highlights that although primary carcinoma of gall bladder are known for their late presentation and hence poor survival rates; occult carcinoma GB diagnosed incidentally on histopathological examination of post-cholecystectomy specimen are usually detected at earlier stages and thus should have better prognosis.

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