ORIGINAL ARTICLE

CARCINOMA OF GALLBLADDER: ITS FREQUENCY AND CLINICAL PRESENTATION IN TWO HUNDRED CASES OF CHOLELITHIASIS

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ABSTRACT

Background: Primary carcinoma of the gallbladder is the most common biliary tract tumor. Although its exact aetiology is not known, gallstones are considered to be an important risk factor for the development of carcinoma of the gallbladder. The objectives of the study were to find out frequency of carcinoma gallbladder in patients suffering from cholelithiasis and the frequency of symptoms, signs, ultrasonographic findings, peroperative and histopathologic findings in patients having carcinoma gallbladder.

Material and Methods: This cross sectional study was carried out in the Surgical Unit of Kohat Development Authority Hospital, Kohat from January 2009 to June 2011. All patients having gallstones were included in this study. Patients unfit for general anesthesia or positive for HBV, HCV or HIV were excluded from the study.

Results: Out of the 200 patients cholecystectomy was possible in 193 patients. The frequency of carcinoma of gallbladder in our study was 4% with female to male ratio of 7:1. The main presenting complaints were pain in the right upper quadrant of abdomen, anorexia, nausea, vomiting, weight loss and jaundice. The main clinical signs were mass in the right hypochondrium (50%) and jaundice (37.5%). 87.5% patients were in stage IV disease. 7 patients had inoperable malignant disease at the time of surgery.

Conclusions: This study concluded that the frequency of carcinoma of the gallbladder is the same as elsewhere in the world but the gallstones disease and carcinoma gallbladder affects comparatively younger female patients of low socioeconomic status.

KEY WORDS: Biliary Tract Neoplasms, Gallbladder, Cholelithiasis, Gallbladder Neoplasms.

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INTRODUCTION

Primary carcinoma (CA) of the gallbladder is the most common biliary tract tumor and the sixth most common cancer affecting the gastrointestinal tract.[1,2] Cholelithiasis is a common, economically significant digestive disease that affects some 10-15% of the global population.[3] The exact aetiology of carcinoma of gallbladder is not known, though gallstones are considered to be an important risk factor for the development of carcinoma of the gallbladder.[4] The presence of gallstones increases the risk of gallbladder cancer four to five fold.[5] The other risk factors for developing gallbladder cancer include chronic infection of the biliary tract, in particular due to Salmonella typhi, chemical exposure, cigarette smoking, high parity, postmenopausal state, diet, and obesity.[6]

The suspicion that gallstones are responsible for the causation of carcinoma of the gallbladder is augmented by the fact that gallstones are present in 65-90% of patients with carcinoma of the gallbladder.[4] Moreover carcinoma of the gallbladder develops in patients with gallbladder preserving therapies for cholelithiasis and that chronic irritation of the gallbladder mucosa by the gallstones leads to dysplasia and carcinoma in situ.[7,8] Most of the patients suspected of carcinoma of gallbladder have advanced disease at the time of diagnosis and they are incidentally diagnosed when a laparotomy is undertaken for the upper gastrointestinal symptoms.[9]

Although it is the commonest malignancy of the biliary tract, it escapes detection due to the fact that carcinoma gallbladder does not have any specific symptoms and signs and early disease is indistinguishable from the gallstones disease.[10]

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The incidence of gallbladder cancer varies greatly in different areas of the world. Highest incidence rates (7.5% per 100,000 for males and 23% per 100,000 for females) are seen in American Indians, people of Chile, South American people and North India.[4] Within a country there are great variations in the incidence in different parts and in different ethnic groups.[11]

Carcinoma of the gallbladder has got poor prognosis. The patients having early disease have good chances of five-year survival with simple cholecystectomy. If prompt surgical resection including extended cholecystectomy is undertaken for T_{1b} or T_2 disease, only then the chances of survival are increased.[12] The objectives of this study were to find out frequency of carcinoma gallbladder in patients suffering from cholelithiasis and the frequency of symptoms, signs, ultrasonographic findings, peroperative and histopathologic findings in patients having carcinoma gallbladder.

MATERIAL AND METHODS

This was a cross sectional study which was carried out in the Surgical Unit of Kohat Development Authority Hospital, Kohat from January 2009 to June 2011.

All patients having gallstones confirmed on ultrasonography and fit for general anesthesia were included in the study. All those patients unfit for general anesthesia or positive for Hepatitis B virus (HBV), Hepatitis C virus (HCV) or Human Immuno deficiency virus (HIV) were excluded from the study. Age grouping was done as: 50-59, 60-69 and 70 and above years.

On admission to the unit, detailed history was taken and thorough general physical and systemic examination was performed and recorded on a proforma along with demographic data of the patient i.e gender, age in years, age group and socioeconomic status. Complete blood counts and serology for HBV, HCV and HIV were done in all patients. ECG and chest x-ray were performed where needed. Each patient was given intravenous Cefuroxime 750 mg half an hour before surgery.

These patients underwent abdominal exploration through standard right subcostal incision. The points noted down in the operation record included presence/absence of gallstones, acutely inflamed adherent gallbladder, chronic cholecystitis, gallbladder wall texture, presence of sludge or stone/s or mass in the gallbladder area or any other incidental findings. Where carcinoma of the gallbladder was encountered, findings related to the staging of the disease were recorded including liver invasion, lymphadenopathy in the porta hepatis, along the biliary ducts, coeliac axis or para aortic region. Peritoneal seedlings of tumour and presence of ascites were also noted. A small sized drain was routinely placed in the gallbladder bed after cholecystectomy.

The gallbladders obtained at cholecystectomy were opened, after the completion of surgery by the operating surgeon and presence of gallstones recorded on the proforma. The gallbladders were preserved in formalin solution and sent for histopathological examination. In patients having advanced carcinoma of the gallbladder, where cholecystectomy was not possible, tissue pieces from the area of malignancy were sent in formalin for histopathological examination. Patients were regularly reviewed in out-patients department at two weeks interval following discharge, where the biopsy reports were also received and entered into the relevant proforma.

Gender, age in years and age grouping were demographic variables. Age (numeric data) was analyzed for mean, SD and range. Gender, socioeconomic status and all the research variables (nominal data) were analyzed for frequency (number) and relative frequency (%).

RESULTS

Two hundred patients with gallstones were included in study. The mean age of the patients with CA gall bladder was 52.57+4.36 (50-84) years. The frequency (number) and relative frequency (%) for age grouping was as:4 (50%) in age group 50-59, 3 (37.5%) in age group 60-69 and one (12.5%) in age group 70 and more years.

The frequency (number) and relative frequency (%) of CA gallbladder was eight (4%) out of 200 gallstone patients. Seven (87.5%) female and one (12.5%) male patient had CA gallbladder with a female to male ratio of 7:1. Seven (87.5%) patients presented with pain in the right hypochondrium, 3 (37.5%) patients with post prandial fullness, 5 (62.5%) patients had associated nausea and vomiting, three (37.5 %) patients had associated jaundice and 5 (62.5%) had anorexia and of loss weight. Tenderness in the right hypochondrium was present in 4 (50%) patients while Murphy's sign was positive in one (25%) patient. Twenty five percent of patients had no positive clinical findings on presentation.

In patients having CA gallbladder, the haemoglobin percentage of one (12.5%) patient was below 8 g/dl, 6 (75%) patients had haemoglobin percentage between 8 and 10 g/dl while one (12.5%) had haemoglobin in the range of 10-12 g/dl. None of the patients had haemoglobin percentage above 12 g/dl.

Abdominal ultrasonography was done in each of the 200 cases with gallstones. 125 (62.5%) pa-

Table: Comparison of Clinical Presentations.

Studies	Abdominal pain	Nausea, vomiting	Fever	Weight loss	Anorexia	Jaundice	Palpable Mass
Our Study	87.5%	62.5%	25%	62%	625%	37%	50%
Shaikh SM[18]	100%	80%	30%	40%	20%	40%	20%
Sultan N[19]	96%	60%	—	—	—	—	40%
Wanebo HJ[23]	79%	53%	—	—	—	34%	54%
Collier NA[24]	60%	—	—	—	—	74%	—
Misra NC[4]	82%	68%	—	72%	74%	44%	65%

tients had distended while 75 (37.5%) patients had contracted gallbladders. Half of the patients had thick walled gallbladders while the other half of them had normal walled gallbladders. All of the patients had their gallstones detected by ultrasonography; 174 (87%) had multiple gallstones while 26 (13%) patients had a single gallstone of 2.5 cm size. In one patient (12.5%) tumour invasion of the liver bed was detected by ultrasonography.

One hundred and ninety three patients underwent cholecystectomy for cholelithiasis. A total number of 193 gallbladders and seven biopsy specimens were sent to the histopathological examination. 60 (30%) patients were reported to have acute cholecystitis, 132 (66%) chronic cholecystitis while 8 (4%) patients were reported to have carcinoma of the gallbladder. All of these were adenocarcinomas.

One patient who had early disease diagnosed on histopathological examination and simple cholecystectomy was considered sufficient. Seven (87.5%) patients had stage IV disease where only palliative treatment in the form of biliary enteric bypass was performed.

DISCUSSION

The higher incidence of occurrence of the disease at a comparatively younger age is noticeable in our study. This is in accordance with the results of the Pakistani workers. According to Ahmed I, the mean age for males was 54.3 years and 50.5 for females.[13] Uddin A has described the incidence of occult malignancy as 5%, while retrospective studies conducted by Pakistan Medical Reasearch Council, Islamabad, Pakistan and Jinnah Post Graduate Medical Center, Karachi, Pakistan (1980) had produced figures of 8.4% and 6.6% respectively.[14] Haroonwala Z G et al and Yaqin HU have reported frequency ranging from 5.8% to 8.7%.[15-17] Sheikh S.M has reported frequency of 10%.[18]

The higher occurrence of carcinoma of the gallbladder in Pakistan can be explained by the delay in diagnosis of gallstones due to lack of basic health education. Moreover, quackery, superstitions and scarcity of diagnostic health facilities make early diagnosis of gallstones difficult which leads to recurrent attacks of cholecystitis and this causes metaplasia of the gallbladder mucosa and later on predisposes it to malignant changes.

The female to male ratio of 7:1 is also quite comparable to a study in Pakistan by Sultan N et al who have reported female to male ratio of 6.5: 1.[19] Sheikh S.M et al have reported a ratio of 1.5:1 while Cubertafond P et al have reported a female to male ratio of 3.5:1.[18,20] The results of the last two studies are quite in contrast to our study wherein the disease as compared to males much more predominantly affects the females.

In our study the highest age occurrence of the disease was in the fifth decade. This is in accordance with the results of Shaikh S M et al but is in sharp contrast to the studies and surveys in the developed countries, where the disease is more common in the seventh decade as recorded by Strauch GO and Parakevopoulos.[18,21,22] Occurrence of carcinoma of the gallbladder at a younger age, in this part of the world in comparison to the Western countries, is also related to our social setup, where marriages of females take place at an early age and greater numbers of children are born. Bile becomes more lithogenic during the childbearing age and so in our women the process of stone formation and its related consequences start at an early age.

Majority of the patients in our study (87.5%) belonged to lower to middle socioeconomic group, while only 12.5% belonged to upper class of the society. Shaikh SM has recorded that 90% of the affected patients belonged to poor families.[18]

In our study 100% patients having carcinoma of the gallbladder had gallstones, which supports the hypothesis that cholelithiasis initiates the chain of events leading to carcinoma of the gallbladder.

The comparison of the clinical presentation of our study with other studies is shown in the Table. It shows that the clinical presentations in our study are quite similar to other studies in Pakistan and also with studies from other parts of the world.

Among the laboratory investigations, haemoglobin percentage had important relevance to the extent of the disease. 87.5% of patients suffering from carcinoma of the gallbladder had a haemoglobin percentage of below 10 gm/dl with only 12.5% having haemoglobin between 10-12 gm/dl. None of them had hemoglobin of above 12 gm/dl. The low haemoglobin of the patients was due to the fact that 87.5% of the patients had stage IV disease. Moreover, the majority of these patients belonged to poor families, which resulted in poor nutrition because of poverty and lack of education.

In our study the pre-operative diagnosis of CA gall bladder with the help of ultrasonography was possible in 50% patients only. Shaikh SM has recorded 30% disease detection by preoperative ultrasonography.[18] Chijiiwa K et al have recorded 80% success in the detection of the disease by ultrasonography in their studies.[25] Chaudhry et al in their study of 30 cases of carcinoma of the gallbladder have reported a diagnostic accuracy for ultrasonography as 47%.[26]

The histopathological examination of the gallbladders and biopsy specimens confirmed carcinoma of the gallbladder in 4 percent of the patients suffering from cholelithiasis.

In this study 87.5% of the patients at the time of the diagnosis were in stage IV disease. The reason for the late diagnosis of the disease is that the early disease is quite indistinguishable from the benign gallstone disease and that the non-specific clinical features of the disease disguises its early presentation. Moreover, lack of high-resolution ultrasonography equipment or expertise may be another cause.

Only 12.5% of our patients had curative resection as compared to 23% reported by Cubertafond P et al.[20] This difference can be explained by the fact that in our study only one patient had stage I disease for which simple cholecystectomy was sufficient whereas Cubertafond P et al analyzed data in which 108 patients had T_1 to T_2 lesions. 87.5% of our patients received palliative treatment. This included biliary enteric bypass or placement of a cholecystostomy tube to relieve obstructive jaundice. Cubertafond P et al reported palliative treatment in 77% cases as compared to 87.5% in our study. This is because most of our patients at the time of diagnosis were in an advanced stage of the disease and could not be offered curative treatment.

CONCLUSIONS

This study concluded that the frequency of carcinoma of the gallbladder in cases of gallstones was 4% and that carcinoma of gallbladder occurred at an early age in this part of the world with females being much more predominantly affected.

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CONFLICT OF INTEREST
Authors declare no conflict of interest.
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None declared.