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Pathology

Clinicopathological Study of Gall Bladder Carcinoma: A Six Year Study

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Abstract **Original Research Article**

Carcinoma of gall bladder is uncommon malignancy having high mortality and low five year survival rates. Gallbladder carcinoma (GBC) is the commonest cancer of the biliary tree and the most frequent cause of death from biliary malignancies. The incidence of GBC shows prominent geographic, age, race, and gender-related differences and is higher in patients with gallstones. This prompted us to study the clinicopathological aspects of the disease and the incidence of gallstones in gallbladder carcinoma patients. In this, combined retrospective (January 2009 to April 2013) and prospective (May 2013 to December 2015) study of six years, 80 patients of gallbladder carcinoma (14 males and 66 females), (range 22-79 years; mean 48 years) were studied. Most of the patients presented with abdominal pain and mass, with jaundice. Gallstones were present in 86% of patients. Adenocarcinoma (72 %) was the commonest histological type. The study indicates that GBC is common in our scenario. It is a disease of females, has a strong association with gallstones and every cholecystectomy specimen should be examined histopathologically.

Keywords: Gall bladder carcinoma, clinicopathological, histopathologically.

INTRODUCTION

Carcinoma of the gall bladder, overall, is the most common cancer of the biliary tract and one of the highly malignant tumors with poor prognosis [1]. It is the fifth most common gastrointestinal malignancy following colon, pancreas, stomach and oesophagus [2]. Incidence increases with age. Almost 90% patients are 50 years of age or older at the time of diagnosis. Carcinoma of the gallbladder is a disease of elderly women, with a female to male ratio of about 3.2 to 1[3]. Gall bladder cancer is very common in South American countries, the Mediterranean region, Japan and northern parts of India [4]. Chile has the highest incidence rate of gallbladder cancer (7.5/100,000) especially among American females [5]. According to the Indian Council of Medical Research cancer register, in the north the incidence of gallbladder cancer is 2.5-8.5/100,000 female and 1.6-3.7/100,000 in males whereas in southern India it is only 0.7-0.8/100,000 female and 0.5-0.6/100,000 male population [6].

The etiology of gallbladder cancer has been a source of speculation. The incidence of GBC parallels the prevalence of gallstone disease; large and longstanding gallstones being associated with a higher risk of GBC. The risk of GBC in patients with gallstones has been reported to have increased four to seven times [7]. The association between an abnormal pancreatobiliary duct junction, a porcelain gallbladder, and other biliary disorders such as choledochal cyst, primary sclerosing cholangitis, Mirrizi's syndrome and gallbladder cancer has also been recognized [8].

Primary carcinoma of the gallbladder is an unexpected histopathological finding in 1-3 % specimens after elective cholecystectomy for benign gall bladder disease. The overall prognosis has remained dismal with the 5-year survival of 5-10% due to the late detection of the disease [9]. Prior to the era of ultrasonography and CT scanning, the rate of the correct pre-operative diagnosis was only 8.6%, which has improved considerably to 75–88%, with the use of these newer imaging techniques. Still, a pre-operative diagnosis of early carcinoma of the gall bladder is seldom made, where the 5-year survival is 91-100%[10].

The most common clinical manifestations of gallbladder carcinoma are right upper quadrant abdominal pain and anorexia, and the most common abnormal laboratory finding is elevated alkaline phosphatase level[11].

As the tumor progresses gall bladder may fill with tumor or may contain pus, mucus or stones. Gallbladder carcinomas usually also contain calculi (80-90% cases) and exhibit marked fibrosis of the wall. The fact that some gall bladder carcinomas are not obvious on gross examination indicates the need for microscopic examination of every excised gallbladder [12].

Microscopically most carcinomas of the gallbladder are adenocarcinomas (80-95%), and can be papillary, tubular, and mucinous or signet cell type and less common include: undifferentiated or anaplastic carcinoma (2-7%), squamous cell carcinoma (1-6%), and adenosquamous carcinoma (1-4%). Carcinoid tumors, small – cell carcinomas, malignant melanomas, lymphomas and sarcomas are particularly rare [13].

The objectives of the present study were: 1) to study the clinicopathological aspect of the disease in patients of gallbladder carcinoma in Rohailkhand area. 2) To know the incidence of gallstones in these patients of gallbladder cancer.

This was a combined retrospective (January 2009 to April 2013) and prospective (May 2013 to December 2015) study entitled "Clinicopathological study of gall bladder malignancy"

A six year study was conducted in the department of pathology, SRMS IMS, Bareilly. Cases of histologically proven gall bladder malignancies from January 2009 and December 2015 were included.

Variable parameters analysed for each case included age, sex, site, histopathological diagnosis, presence or absence of gallstones. A total of 80 patients were selected. All the relevant clinical details including detailed history, physical examination, ultrasonographic (US), computed tomography (CT) scan of whole abdomen and laboratory reports were retrieved of these patients.

RESULTS

The present study included 80 cases of histopathologically proven cases of gall bladder malignancy. The table shows sex distribution in patients of gall bladder malignancy.

Table-I: Sex distribution

Sex	Number of malignant cases	(%)
Male	14	17.5%
Female	66	82.5%
Total	80	100

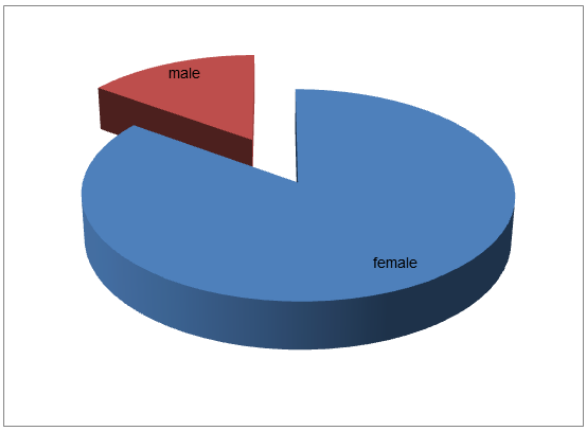

Fig-1

Total number of patients were 80 out of which 66(82.50%) were females and 14(17.5%) were males (fig 1). There was female preponderance with a ratio of M:F=1:4.7

The table shows age distribution of patients with gall bladder malignancy.

Table-II: Age wise distribution

Age	Total cases	Percentage	Gender	
	CASES		Males	Females
20-30	3	3.75%	0	3
31-40	17	21.25%	3	14
41-50	31	38.75%	6	25
51-60	19	23.75%	1	18
61-70	9	11.25%	3	6
71-80	1	1.25%	1	0
	80	100	16	64

MEAN AGE=48.4 years

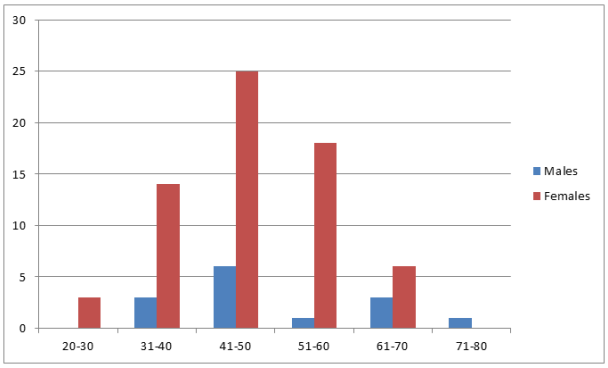

Fig-2

It was observed that maximum number of patients were present in 41 years to 50 years of age group i.e 31(38.75%), with female preponderance

followed by minimum cases i.e 1(1.25%) in 71-80 years.

The table shows the association with stones in the patients of gall bladder malignancy.

Table-III: Number of patients associated with cholelithiasis

Stones	No. Of cases	%
Stones present	69	86%
Stones absent	11	14%
Total cases	80	100

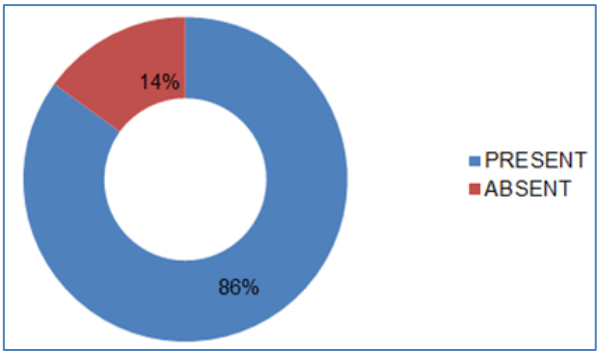

Fig-3

Stones were present in 86 (%) of cases and absent in 14(%) of cases (fig3).

The most common presenting features were pain in right hypochondrium in 46 patients (57.5%) , abdominal mass in 18 patients (22.5%) and jaundice in16 patients(20%).

Table-IV: Number of patients with signs and symptoms:

FINDINGS	NUMBER OF PATIENTS	PERCENTAGE
PAIN IN RIGHT HYPOCHONDRIUM	48	57.5
ABDOMINAL MASS	18	22.5
JAUNDICE	16	20

The table shows types of malignancy in gall bladder.

Table-V: Type of malignancy

Types	No. of cases	Percentage
1. Adenocarcinoma	72	90%
2. Squamous Cell Carcinoma	4	5%
3. Adenosquamous	2	2.5%
4. Neuroendocrine	1	1.25%
5. Spindle Cell	1	1.25%
Total	80	100

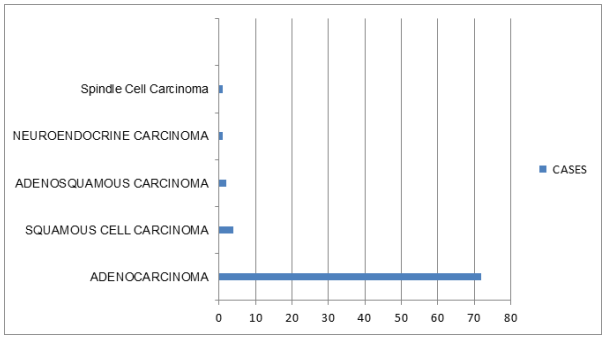

Fig-4

It was observed that there were significantly higher number of patients with adenocarcinomas 72(90%), followed by squamous cell carcinoma 4(5%), adenosquamous carcinoma 2(2.5%) and 1 case each of neuroendocrine carcinoma (1.25%) and spindle cell carcinoma (1.25%) (Fig-4).

DISCUSSION

Gallbladder Carcinoma (GBC) is the most common malignancy of the biliary tract and the third most common malignancy of the gastrointestinal tract worldwide.[14] Gallbladder cancer is the most common cause of death from biliary malignancies [15]. It is usually detected at an advanced stage due to its nonspecific symptoms [16].

It is rare in the western world, including the USA, UK, Canada, Australia and New Zealand, where the incidence rates range between 0.4 and 0.8 in men and between 0.6 and 1.4 in women per 100,000 population. However, high incidence rates, up to 2–4 in men and up to 4–6 in women, have been reported from various countries in central and South America, central and eastern Europe, and Japan. In Chile, GBC is the leading cause of death from cancer among women [17].

In India, cancer of gallbladder shows varying geographic distribution, as the incidence is much higher in North India as compared to South India. Though the overall age-adjusted incidence rates of GBC in India are low (1.0 for men and 2.3 for women per 100 000 population), the incidence in women in Delhi in north India and Bhopal in central India is as high as 6.6 and 5.2, respectively, much higher than 0.6 in Chennai and 0.8 in Bangalore in south. Gallbladder cancer ranks among the first five common cancers in females in

Delhi, India.[18] In the endemic zone of West Bihar and Eastern Utter Pradesh; it is the third most common malignancy of the alimentary tract [19].

Our study comprised 80 patients, out of which 64 (82.5%) were females and 16(17.5%) were males with F: M ratio 4.7:1. Shukla *et al*. [19] in their sixteen years experience on 315 cases of gall bladder carcinoma and, Panday et al in their study on 99 cases of gall bladder malignancy [20] reported F: M ratio 3:1 and 2.5:1 respectively, which was in concordance with our study. However Liang at el in their twenty five years' experience reported, male to female ratio of 1:1[21].

Roa *et al*. in their prospective study of six-hundred-sixty-nine cases of gallbladder carcinoma 557 were females (83.5%) and 112 were males (16.5%)[22].

In the present study the mean age of the patients was 48 years with an age range of 26-79 years. Maximum patients i.e 31 (36.7%) were in fifth decade of life. Similar results were found in a study conducted by Hamdani *et al*. on 198 patients where, the mean age was 55 years, with a range of 28-82 years and fifth decade was the peak age of presentation [20].

In a study conducted by Lancet lobo *et al*. on 50 patients of GBC in a tertiary hospital of Bombay, mean age was 54 years and their ages ranged from 25 years to 80 years [23]. In contrast, studies from west reported the mean age of 67 years [24] and the peak age of incidence in 7th decade of life [25].

The commonest factor implicated in the gallbladder carcinogenesis is gallstones. According to WHO, 80% of gall bladder malignancies are associated with cholelithiasis. In our study 69(86%) patients had presence of gall stones. A study by Giang *et al*. on 23 cases of GBC showed presence of gall stones in 60% cases [26].

A study from north India [19] on 99 cases of GBC showed presence of gall stones in 70% cases. Another study by Black *et al*. found gallstones in 41 out of 56 patients of south western American Indian origin with an incidence of 73.2% [27]. In a study [28] from Chile, an area of high incidence of GBC, gallstones were found in 53 out of 54 potentially resectable GBC patients.

The above studies favour a causal association between gallstones and GBC. It has been shown that chronic trauma and inflammation can induce epithelial dysplasia, carcinoma in situ and invasive cancer but a cause and effect relation has not been unequivocally proved [29]. Furthermore, one would expect squamous cell carcinoma to develop as a result of chronic irritation whereas it is adenocarcinoma which is the commonest histological type of carcinoma gall bladder seen in over 90% of case [30]. In our study 72(90%) patients were diagnosed with adenocarcinomas. The preponderance of gall bladder adenocarcinoma was followed by 4 cases of squamous cell carcinoma, 2 cases of adenosquamous carcinoma and one case each of neuroendocrine carcinoma and spindle cell carcinoma. In a study conducted by Beltz *et al*. on 117 patients of GBC 84% cases were adenocarcinomas [24]. A study conducted by kalita et al on 25 cases of GBC, found 20(80%) cases of adenocarcinoma not otherwise specified (with well, moderate and poor differentiation), mucin secreting adenocarcinoma in 2(8%) cases, single case (4%) each of papillary adenocarcinoma, adenosquamous carcinoma and adenocarcinoma with areas of hepatoid differentiation[31]. In a study conducted by Roa et al squamous cell carcinomas and adenosquamous carcinoma were rare [32].

Gall bladder cancer patients are generally asymptomatic for a long time or present with very non-specific symptoms. Commonly, these symptoms are related to associate gallstones Shiwani *et al.,* 2005. In our study, abdominal pain (88.9%) followed by abdominal mass (76.3%) and jaundice (60%) were the most common presenting features. Consistent results were reported in other studies (Gupta *et al.,* 2004; Khan *et al.,* 2010).

In conclusion Gall bladder cancer is more prevelant in india as compared to western countries and more common in women. Females in forties and fifties presenting with a history of recent onset of constant pain in the right hypochondrium or lump and jaundice should be thoroughly evaluated. In spite of the recent advances in the field of imaging, the detection of gall bladder cancer in early stages remains low. Therefore, owing to strong association of gall stones with gallbladder carcinoma, attempts should be made to convince the patients for an early cholecystectomy followed by histopathological examination of all surgically resected specimens so that gall bladder cancer can be detected at an early, potentially curable stage.

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