Clinicopathological evaluation of gallbladder carcinoma with special emphasis on incidentally detected cases- A hospital based study

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Abstract

Introduction & Objectives: The gallbladder carcinoma is highly aggressive tumour and is the sixth among GI tract–related organs. Its incidence is much higher in North and North-Eastern population as compared to South India. As they mimics' gallstone diseases, it is likely to find gallbladder carcinomas incidentally during surgery for cholecystitis or other benign lesions. Objective of our study is to find out the percentage of incidental gallbladder carcinoma and to analyze the gallbladder carcinoma cases.

Materials and Methods: The present study was undertaken at a tertiary care hospital in Dibrugarh, over a period of one year. We had given utmost importance on the grossing of the gallbladder specimens as we were emphasizing on incidentally detected gallbladder carcinoma cases.

Results: Among 302 cholecystectomy specimens, 29 cases of primary gallbladder carcinoma were detected, out of which 8 were incidental (2.65%). Association with gall stones were found in 26 cases (89.7%).

Interpretation & Conclusion: Discarding the gallbladder specimens without histopathological analysis should best be avoided. Selective approach for sending these specimens to the laboratory may result in missing discrete pathologies.

Keywords: Gallbladder carcinoma, Gallstone disease, GI malignancy, Incidental GBC, North-East.

Introduction

The gallbladder carcinoma is the sixth among GI tract–related organs and most common site within the biliary tract[1] and is characterized by very high mortality rate and rapid progression. Detection at early stage indicates prolonged survival and a very good prognosis, yet late diagnosis and absence of effective treatment for many patients remains typical feature of this disease.

Gallbladder cancer is at least twice more common in women than in men; this gender disparity can be several folds greater in regions of highest incidence. The highest incidences are reported in Chileans, Bolivians, Indians, Pakistanis, Central Europeans, and Americans of Mexican origin.[2] In India, GBC is most prevalent in the northern and north-eastern states of Bihar, Uttar Pradesh, Orissa, West Bengal and Assam.

According to data published by Indian Council of Medical Research (ICMR), in the Dibrugarh District of Assam, gallbladder has appeared as the 7th leading site of cancer among males during 2012-2014, while in females gallbladder has replaced cancer of the cervix uteri as the second leading site.[3]

The most important risk factor for gallbladder malignancy (besides gender and ethnicity) is gallstones which are present in 95% cases. However, only 1-2% of patients with gallstones develop gallbladder cancer. In Asia, chronic bacterial or parasitic infections have been implicated as risk factors, and coexistence of gallstones with gallbladder cancer is much lower. Nonetheless, the common thread that ties gallstones or chronic infections together with gallbladder cancer is chronic inflammation.[4]

Clinical presentation of benign gall bladder disease and gallbladder malignancy is almost similar and most of the times it is masked by chronic cholecystitis. Preoperative diagnosis of carcinoma of gallbladder occurs only in fewer than 20.0% of patients.[5] Hence, it is very likely to find gallbladder tumours incidentally during surgery done for stones or biliary tract diseases. Incidental detection of gallbladder carcinoma in cholecystectomy specimen has been reported in 0.3-2% of all cholecystectomy performed for benign conditions.[6]

Aim of our study is to find out the percentage of incidental gallbladder carcinoma and to analyze the gallbladder carcinoma cases.

Materials and Methods

The present study was undertaken in Dibrugarh, at a tertiary care hospital over a period of one year from June 2014 - May 2015. Detailed clinical data & laboratory investigations were collected from medical records in surgically resected specimens. Radiological reports available with the patients were examined for obtaining preoperative suspicion and intraoperative diagnosis were obtained from surgeons' OT notes. We had given utmost importance on the grossing of the gallbladder specimens as we were emphasizing on incidentally detected gallbladder carcinoma cases. Haematoxylin and eosin stained sections were examined and tumours were typified according to recent WHO guidelines and AJCC tumour staging system.

Results

During the period from June 2014 to May 2015, total 302 cholecystectomy specimens were received, including laparoscopic, open cholecystectomy and partially resected specimens.

While most revealed benign pathology, including chronic calculus cholecystitis (with mild to severe non specific inflammation) and with specific changes like eosinophilic, follicular, xanthogranulomatous cholecystitis, cholesterolosis, etc. Adenomyomatosis and pyloric gland metaplasia were also noticed.

Out of these 302 cases, 33 were diagnosed as malignant gallbladder lesion, among which 29 cases were primary carcinoma, 3 metastatic adenocarcinoma and one neuroendocrine tumour (G2) were detected.

Among the 29 primary gallbladder carcinoma cases; there were 23 (79.3%) females and 6 (20.7%) males with definite female preponderance. Male: female ratio of 1:3.8 was found in the study. The age of all patients ranged from 20 to 80 years with a mean age of presentation of 47.8 years (Mean ± SD = 47.8 ± 12.03). Majority of the cases were in the 4^{th}, 5^{th} & 6^{th} decades.

The most common presenting symptoms in the primary gallbladder carcinoma cases were pain in epigastrium and right hypochondrium in 24 patients (82.8%) and anorexia, nausea/vomiting in 20 (68.9%) and 13 (44.8%) cases respectively. Abdominal tenderness and mass were found in 16 (55.2%), and 6 (20.7%) cases respectively.

Focal/diffuse gallbladder wall thickening was noted in 8 (27.59%) cases on ultrasonography, while wall thickenings due to mass lesion or polyp were noted in 9 (31.03%) primary gallbladder carcinoma cases. Ultrasonography showed nonspecific thickened wall in 4 (13.79%) cases and oedematous wall in 1 (3.45%) cases, while 7 (24.14%) cases showed gallbladder wall thickness within normal limit.

During the operative procedure gallbladder mass lesions were noted in 11 (37.93%) cases, while mass lesion with associated features of cholelithiasis and empyema were seen in 8 (27.59%) and 2 (6.89%) cases respectively. Seven (24.14%) cases showed features of cholelithiasis and 1 (3.45%) case showed features of empyema.

So, out of 302 cholecystectomy specimens, 8 (2.6%) cases were not suspected on radiological investigations or intraoperatively, i.e.incidentally detected.

Association with gallstones were found in 26 (89.7%) cases while, among incidentally detected cases all (100%) were associated with gallstones

During grossing, diffusely thickened gallbladder wall were noted in 11 (37.93%) cases, while 5 (17.24%) cases showed focal wall thickening. Polypoidal growths were noted in 8 (27.59%) cases and exophytic/fungating growths were seen in 4 (13.79%) cases. One case (3.45%) showed no obvious abnormality on gross examination.

Fundus, body and neck were involved in 7 (24.14%), 9 (31.03%) and 8 (27.59%) cases respectively, while diffusely thickened gallbladder was found in 5 (17.24%) cases.

Histopathological typing 16 adenocarcinoma cases, out of which 11 (37.93%) were of biliary type, 4 (13.79%) intestinal and 1 (3.45%) mucinous type of adenocarcinoma. Ten (34.48%) cases of intracystic papillary neoplasm with invasive adenocarcinoma component were found, while 1 each of squamous cell, adenosquamous and undifferentiated carcinomas were noted.

Among them 20 (68.97%) were found to be well differentiated, 7 (24.13%) moderately differentiated and 1 (3.45%) each of poorly and undifferentiated cases were noted.

Invasion into the lamina propia was noted in 5 (17.24%) cases, while infiltration upto the muscle layer, perimuscular connective tissue and serosa were observed in 13 (44.83%), 9 (31.03%) and 2 (6.90%) cases respectively.

On T-staging, 13 (44.83%) cases were found to be in T1b stage, while 5 (17.24%) cases were in T1a stage and 6 (20.69%) were in T2 stage. Five (17.24%) cases that were in T3 stage were also noted among primary gallbladder carcinomas. 37.5% of incidentally detected carcinomas were in T1a, while 37.5% were found in T1b stage.

Fig. 1: Gallbladder carcinoma showing scirrhous type of growth

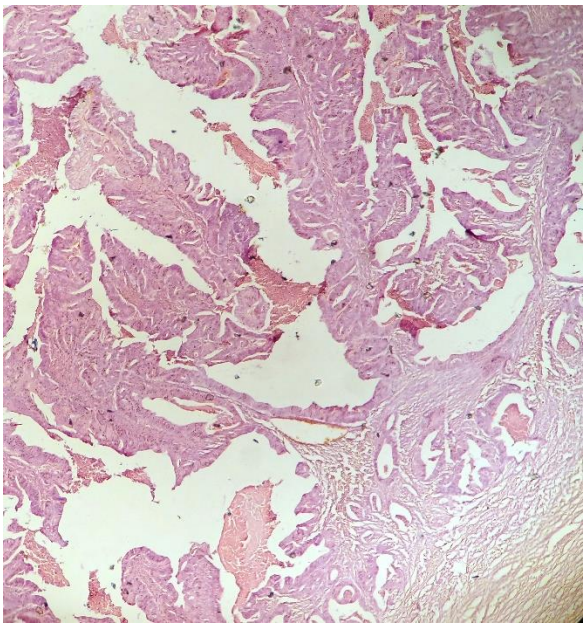

Fig. 2: Intracystic papillary neoplasm with invasive adenocarcinomatous component into lamina Propia 40X

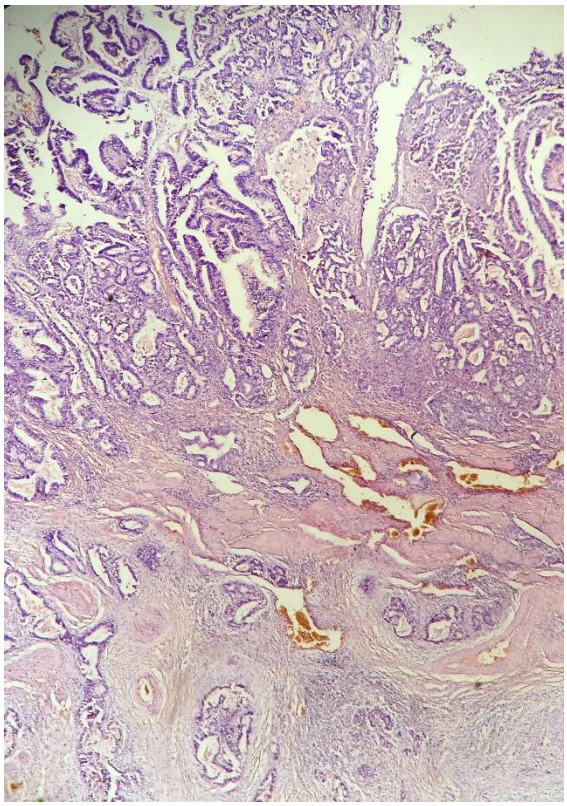

Fig. 3: Intracystic papillary neoplasm with invasive adenocarcinomatous component into perimuscular tissue 10X

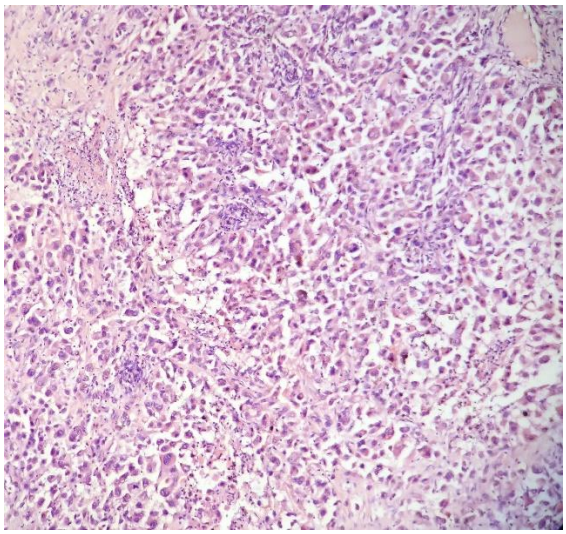

Fig. 4: Undifferentiated gallbladder carcinoma 10X

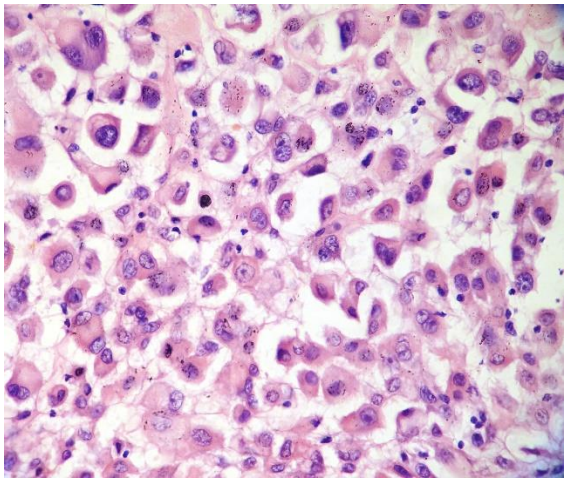

Fig. 5: Undifferentiated gallbladder carcinoma 40x

Discussion

Gallbladder cancer is the most common cause of death from biliary malignancies (Khan et al., 2010).[7] Most patients of gallbladder carcinoma are older than 50 years, with the mean age older than 64 years. The present study revealed the mean age of the patients to be 47.8 years, with a minimum and maximum age of presentation was 26 years and 71 years. The mean age of presentation for females and males were 45.4 and 56.8 years respectively. Majority of the cases were in the 4th, 5th & 6th decades. In the Dibrugarh district, where gallbladder carcinoma was the 2nd commonest cancer among females, a definite trend shift towards involvement of younger female population could be observed from this study.

In the study conducted by Kalita et al., 2013 shown that mean age of presentation was 54 years, with peak (32%) in sixth decade and a significant number (28%) in fourth decade,[8] while Hamdani et al. (2012) revealed the mean age of the patients to be 55 years.[9] These variations may represent the regional disease patterns and increasing detection rate at early age may be due to increasing awareness and accessibility to health care facilities.

Incidental Gallbladder Carcinoma

Incidental GBC (IGBC) refers to GBC detected for the first time on histopathological examination (HPE) of a gallbladder removed for presumed (clinical, ultrasound, operative) diagnosis of gallstone disease (GSD) and is not suspected before or at operation and even on examination of the opened gallbladder specimen by the surgeon. Practically, all gallbladder carcinomas not detected preoperatively or not diagnosed during or following surgery are considered as IGBC.[10]

Almost 50% of GBC are detected incidentally after surgery for benign disease.[11] The incidence of IGBC has been reported to range from 0.3–1.5% in various series.[12] As the number of cholecystectomy operations increase, it is likely that the number of incidentally discovered GBC will also increase.

Table 1: Incidentally detected gallbladder carcinoma cases in the study population (N= 302)

Types of detection	Number	Percentage
Incidental detection during Histopathological examination	08	2.6%
Suspected/or Diagnosed radiologically or intraoperatively	21	6.9%
Total primary gallbladder Carcinoma cases	29	9.6%

Table 2: Comparison of findings in other studies

Studies	Year	No. of IGBC cases	Total no. of Cholecystec-tomized cases	Incidence rates
Shrestha et al.	2010	9	668	1.4%
Ghimire and collegues	2011	10	783	1.28%
Hamdani et al.	2012	7	198	3.5%
Siddiqui et al.	2013	6	220	2.7%
Kalita et al.	2013	18	4115	0.44%
Waghmare and Kamat	2014	7	270	2.59%
Munshi et al.	2015	9	500	1.8%
Present study	2015	8	302	2.65%

Histological examination of gallbladders (GB) removed during cholecystectomy is routine in most pathology departments. Necessity of histopathological examination of all gallbladder specimen removed for clinically and radiologically benign conditions is controversial. Some authors have suggested that it should be selective[13,14] however several studies have accepted its importance for early detection of this highly aggressive cancer.[9] and that early diagnosis with timely radical surgery are directly correlated to the prognosis of the patients.[15]

KF Chin (2012),[16] Madiha Sajjad (2012),[17] Mittal et al. (2010), had opted for a more selective policy of histological examination of the gallbladder specimens and recommended for examining only the macroscopically abnormal gall bladders. However, preoperative imaging findings and intraoperative gross examination may not be reliable in identifying malignancy in all cases.[18,19]

The Royal college of pathologists in their report titled "Histopathology and cytopathology of limited or no clinical value" recommended examination of all gallbladder specimens, as significant pathology may be present with normal gross morphology.[20]

All below mentioned studies also supported their views and recommended that routine histological examination of every cholecystectomy specimen should be done regardless of macroscopic appearance of gallbladder.

In the present study, out of 302 cholecystectomy specimens, 8 (2.65%) cases were incidentally detected i.e. not suspected on radiological investigations or intraoperatively.

The signs and symptoms of gallbladder cancer are nonspecific, mimicking chronic cholecystitis (pain, anorexia), and manifest only after the tumour has inflicted substantial damage.[21] Our study findings also highlighted the overlapping of presenting clinical features between the study population and the primary gallbladder carcinoma cases, which were similar to that of Hamdani et al.

Although the presence of early lesions in the form of focal gallbladder wall thickening or lesions of small mass can be detected by an expert radiologist, not all cases of early GBC present with an obvious lesion on abdominal ultrasonography.[22] When GB contains stones, it is difficult to detect a focal area of thickening or small mass lesions on abdominal US. On ultrasonography (USG) examination, 40-60% cases can be detected only when there is a solid intraluminal mass (Levy et al., 2001).[23]

In our study too revealed that radiological findings were suggestive of gallbladder neoplasm, only in 17 cases out of 29, while in other 12 they were inconclusive.

Agarwal and his collegues, in their retrospective analysis (2012) examined 503 cholecystectomy specimens removed for presumed diagnoses of GSD over a period of 2 years showed that 33 patients had intraoperative suspicion of malignancy and those gallbladders had been sent for frozen-section examination. Of these, only five had evidence of malignancy. The remaining 470 specimens in which there was no suspicion of malignancy macroscopically, GBC was diagnosed in four cases.[10]

When GBC is diffuse, the gross distinction from chronic cholecystitis may be difficult. Gallbladder carcinomas containing calculi exhibit marked fibrosis of the wall, which may represent a reaction to the tumor or the expression of a preexisting chronic cholecystitis. The fact that some gallbladder carcinomas are not obvious on gross examination indicates the need for microscopic examination of every excised gallbladder.[24]

In the present study, during the operative procedure, it was observed that 8 (27.6%) cases were not suspected to be malignant during intraoperative procedure and ultrasonography too inconclusive in diagnosing these cases. These 8 were incidentally detected gallbladder carcinoma cases, found in our study.

Shrestha et al. (2010) showed that combined preoperative and intraoperative findings failed to detect 45.0% of malignant cases in their study.[19]

The association between cholelithiasis and gallbladder cancer has been known since 1861.[25,26] Gallstone is the commonest factor implicated in the genesis of gallbladder

carcinoma. Cholesterol stones, represent approximately 80 to 90 percent of all, in the Western world are considered to be a promoting factor for gallbladder carcinogenesis.[27]

Tyagi et al. (2008) observed that there was an elevated risk for GB cancer for the patients with cholithaiasis.[28] Our study showed presence of gallstones in 26 cases (89.7%). All the cases of incidentally detected carcinomas were seen in association with stones.

Shrestha et al. (2010) reported, presence of gallstones in both benign and carcinomatous cases with frequency of 91.0% (503/550 cases) and 80.0% (16/20 cases) respectively in their study.[19]

Present study showed that among the incidentally detected cases 5 (62.5%) cases showed focally thickened gallbladder wall, 2 (25%) showed diffuse thickening, while one (12.5%) showed no obvious abnormality on gross examination (Occult carcinoma).

Kalita et al. (2013), in their study found diffuse thickening of the wall in 8 (44.44%) cases, while localized growth in the form of nodule or focal thickening in 10 (55.56%) cases on gross examination out of 18 unsuspected carcinoma cases.[8]

Most gallbladder carcinomas arise in the fundus (60%) followed by the body (30%);[21] those in the neck (10%) often grow into the cystic duct.[29] However our study showed a slight increase in involvement of body region.

In conclusion, gallbladder cancer is becoming one of the most common cancers among women in north and northeast India. Thus discarding the gallbladder specimens without histopathological analysis should best be avoided, as gallbladder carcinoma is notorious for its way of presentation. Selective approach for sending these specimens to the laboratory may result in missing discrete pathologies like premalignant benign lesions such as porcelain gallbladder, carcinoma-in-situ and most importantly early carcinomas. Clinical signs or symptoms and/or even radiological assessment may not be fruitful in the detection of early gallbladder carcinoma and histopathology remains the gold standard for their detection.

Moreover considering our geographic region, especially after observing the current trends of gallbladder carcinoma as mentioned in the Population Based Cancer Registry of Dibrugarh District, and also considering the benefits of early detection, all the cholecystectomy specimens must sent for routine histopathological examination.

Another bright prospective regarding the gallbladder carcinoma is its expression of HER2/neu. As these tumours are highly aggressive, and considering the fact that research on therapeutic efficacy of tyrosine kinase inhibitors on gallbladder carcinoma are going on, in the near future treatment of gallbladder carcinoma may bring fruitful outcome to the patients.

Conflict of Interest: None.

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