

Incidental gallbladder carcinoma among the patients undergoing cholecystectomy for benign gallbladder disease: Diagnostic utility of routine histopathological examination of the resected gallbladder specimens

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Abstract

Introduction: Gallbladder carcinoma (GBC) is the most common cancer of the biliary tract, fifth most common cancer of gastro-intestinal tract (GIT) worldwide and the most common cancer of the GIT in India. Around 0.2%-3.3% of the GBCs are diagnosed incidentally (incidental-GBC or IGBC) on histopathological examination of the resected specimen after cholecystectomy. Considering the incidence of IGBC and the good prognosis associated with it, differential diagnosis from primary GBC is of utmost importance.

Aim: The current study was aimed to find the incidence of IGBC among the patients undergoing cholecystectomy for benign gallbladder disease and to establish the diagnostic utility of routine histopathological examination of the resected gallbladder specimens.

Materials and Methods: All the resected gallbladder specimens from the patients who underwent cholecystectomy, for benign gallbladder disease (January 2015 to December 2016), clinico-radiologically unsuspected of GBC with the diagnosis of GBC being made for the first time on routine histopathological examination were included in the study. Diagnosis of IGBC was made on formalin-fixed, paraffin-embedded, hematoxylin and eosin stained sections of the resected gallbladder specimens. Pathological staging of carcinoma was done according to the tumor, nodes, and metastases system designed by American Joint Committee on Cancer for staging GBC.

Results: On histopathological examination of all the benign gallbladder specimens, 09/761; 1.2% specimens were having evidence of IGBC. Mean age of the patients diagnosed with IGBC was 63.9±15.9 years. Eight patients (88.9%) had cholelithiasis and chronic cholecystitis, whereas one patient (11.1%) had chronic cholecystitis alone. The mean wall thickness of the gallbladder was 5.1±1.3 mm. On pathological staging, 88.9% of the detected IGBC cases were found to be in surgically resectable stages. The AJCC stages I, II and III were found in 55.6%, 22.2% and 22.2% of the cases respectively. Adenocarcinoma (55.6%) was the most common type of carcinoma detected followed by mucin secreting adenocarcinoma (33.3%) and papillary carcinoma (11.1%).

Conclusion: Despite thorough clinical and radiological examination, cases of IGBC tend to get missed particularly if selective histopathological examination of the resected gallbladder specimens is practiced. We recommend that routine microscopic histopathological examination of all the benign gallbladder specimens should be performed after cholecystectomy particularly in high incidence areas. A multidimensional approach with close clinical liaison between the Department of Surgery, Gastroenterology, Radiology and Pathology, will surely be helpful in early diagnosis and better patient outcome.

Keywords: Adenocarcinoma, Cholelithiasis, Cholecystitis, Malignancy, Neoplasm

INTRODUCTION

The gallbladder is a foregut-derived organ, which is a pear-shaped sac and lies in shallow fossa on the visceral surface of the right hepatic lobe. [1] Gallbladder stores and concentrates the bile, which helps in digestion and absorption of fat from the small intestine. [2] The spectrum of ailments that distress the gallbladder can be congenital, inflammatory or neoplastic in nature [3,4] and often require surgical intervention through cholecystectomy, either laparoscopic or open, as per the demand of clinical condition and preference of the patient. [5]

While inflammatory conditions of the gallbladder pathologies, including acute, chronic, follicular, or xanthogranulomatous cholecystitis are common, gallbladder carcinoma (GBC) remains a relatively rare etiology and is known for its cataclysmic course and poor prognosis. [6-8] However, GBC is the most common cancer of the biliary tract and the fifth most common cancer of gastro-intestinal tract (GIT) worldwide. [8] In India, it is the most common cancer of the GIT. [9] The worldwide incidence of GBC ranges from 0.3%-1.5% [10-12], and the incidence in India ranges from 0.8%-1.0% with central India having the higher incidence as compared to the southern part and even higher along the

gangetic plains of northern India. [5,8,9,] Around 70%-80% of gallbladder malignancies show the presence of gallstone disease (cholelithiasis), and the risk of GBC in patients with the latter has been reported to have increased four to seven times. [13-15] Other commonly observed risk factors include, calcification of gallbladder wall, adenomatous polyp, obesity, estrogen, choledochal cyst, and chemical carcinogens. [5,8,9] Chronic cholecystitis secondary to cholelithiasis can irritate the gallbladder mucosa, thereby triggering the onset of metaplastic and dysplastic transformations, which in turn can predispose the patients to GBC. [7,16] GBC and dysplastic lesions pose a big diagnostic dilemma both clinically and radiologically. They have overlapping features with benign conditions and about 0.2%-3.3% of them are diagnosed incidentally (incidental-GBC or IGBC) on histopathological examination of the resected specimen after cholecystectomy, without any clinico-radiological and intraoperative suspicion of malignancy. [5, 7-9] When compared to non-incidentally or primary GBC, IGBC has a good prognosis, prolonged survival and is a potentially curable disease, provided an adequate surgical strategy is adapted. [17-19] Considering the incidence of IGBC and the good prognosis associated with it, differential diagnosis from primary GBC is of

utmost importance and for that reason; every cholecystectomy specimen should be sent for routine histopathological examination. [19] However, the use of routine or selective histopathological examination of resected gallbladder specimens is still debated.

With the above background, the current study was aimed to find the incidence of IGBC among the patients undergoing cholecystectomy for benign gallbladder disease and to establish the diagnostic utility of routine histopathological examination of the resected gallbladder specimens.

MATERIALS AND METHODS

Study design and study site:

This prospective, cross-sectional study was conducted in the Department of Pathology, S.P Medical College, Bikaner, Rajasthan. All the resected gallbladder specimens from the patients who underwent cholecystectomy, for benign gallbladder disease from January 2015 to December 2016, were received in the Dept. of Pathology of our institution and were analyzed. The study protocol was approved by the Institutional Ethics Committee (IEC).

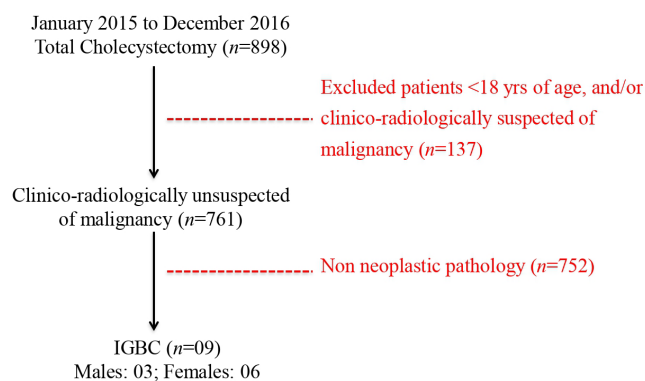
Inclusion and exclusion criteria:

All the laparoscopic and open cholecystectomy specimens of benign gallbladder diseases, clinico-radiologically unsuspected of GBC with the diagnosis of GBC being made for the first time on routine histopathological examination were included in the study. Patients <18 years of age and clinico-radiologically suspected of GBC were excluded. Figure 1 depicts the schematic representation of the patient selection of our study. The study protocol was explained to the participants and prior to their enrollment their written informed consent was obtained.

Sample processing and data collection: Diagnosis of IGBC was made on formalin-fixed, paraffin-embedded, hematoxylin and eosin (H&E) stained sections of the resected gall bladder specimens. Briefly, resected specimens were received in 10% neutral buffered formalin, and after gross examination, multiple sections were taken and were sent for paraffin embedding. Three full thickness sections were obtained from fundus, body and neck of the gall bladder. Additional sections were taken from any grossly abnormal area if present. Sections of 4-5µm thicknesses were cut and stained with hematoxylin and eosin (H & E) for histopathological examination. Pathological staging of carcinoma was done according to the tumor, nodes, and metastases (TNM) system designed by American Joint Committee on Cancer (AJCC) for staging GBC. [20] Demographic details, clinical and radiological (USG and CT scan) information of the patients was collected from the medical Records of the patient.

Statistical analysis:

The data obtained were managed on an Microsoft Excel spreadsheet. Simple descriptive statistics were used to generate frequencies, percentages, and proportions. Wherever relevant, the Chi-square test was used to determine the statistical significance.



IGBC: Incidental gall bladder carcinoma

Figure1: Schematic representation of the patient selection of our study

RESULTS

Over the period of two years (January 2015 to December 2016), a total of 898 cholecystectomy specimens (open, laparoscopic and partially resected) were received, of which 137 (15.3%) were from the patients <18 years of age, and/or clinico-radiologically suggestive of malignancy and hence were excluded. Remaining 761 (84.7%) gallbladder specimens were obtained from patients who underwent cholecystectomy for clinico-radiologically established benign gallbladder disease. In all these patients, despite of the thorough clinical and radiological evaluation, the treating clinician and the radiologist were not suspicious of any kind of GBC.

On histopathological examination of all the benign gallbladder specimens, 09/761; 1.2% specimens were having evidence of IGBC, diagnosed for the first time by histopathological examination without any clinico-radiological suspicion of malignancy. Age of the patients diagnosed with IGBC ranged between 34 to 81 years (mean 63.9±15.9 years). Among the patients diagnosed with IGBC, six patients (66.7%) were females and three (33.3%) were males with a male: female ratio of 1:1.3. A pre-operative USG was done in all the cases and it was found that eight patients (88.9%) had cholelithiasis and chronic cholecystitis, whereas one patient (11.1%) had chronic cholecystitis alone. The mean wall thickness of the gallbladder was 5.1±1.3 mm. On pathological staging most of the detected IGBC cases were found to be in surgically resectable stages like T1a (33.3%), T1b (33.3%), and T2 (22.2%). The AJCC stages I, II and III were found in 55.6%, 22.2% and 22.2% IGBC cases respectively. Adenocarcinoma (55.6%) was the most common type of carcinoma detected followed by mucin secreting adenocarcinoma (33.3%) and papillary carcinoma (11.1%). Figure 2(a-d) depicts the different types of carcinoma detected among the patients diagnosed with IGBC. Table 1 depicts the demographic details, clinico-radiological diagnosis, pathological and AJCC stage, and type of the carcinoma detected among the patients diagnosed with IGBC.

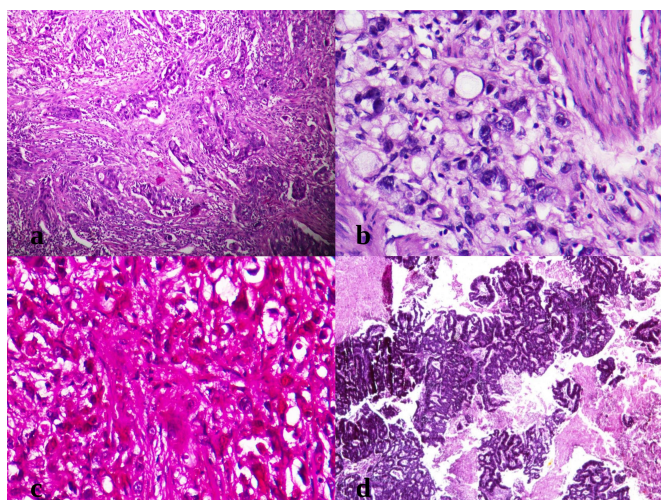


Figure 2: Different types of carcinoma detected among the patients diagnosed with IGBC: a) Adenocarcinoma showing clusters of malignant glands invading the gallbladder wall (H&E, 10X); b) Mucin secreting adenocarcinoma showing tumour cells in clusters, invading gall bladder wall with singlet ring appearance due to intracytoplasmic mucin accumulation (H&E, 10X); c) Mucin secreting adenocarcinoma showing clusters of PAS positive tumour cells invading the gall bladder wall (PAS, 10X); d) Papillary adenocarcinoma showing papillary formation with fibrovascular core covered by malignant cells. It shows cytological atypia with disorganization of the lining epithelium (H&E, 10X).

Table 1: Demographic details, clinico-radiological diagnosis, pathological and AJCC stage and type of carcinoma detected among the patients diagnosed with IGBC.

Cholecystectomy specimens	Number	Percentage
Total gall bladder specimens	898	-
Clinico-radiologically benign gallbladder disease	761	84.7%
Incidental gall bladder carcinoma	09	1.2%
Demographic details (n=09)		
Gender		
• Male	03	33.3%
• Female	06	66.7%
Age (Mean ± SD)	63.9±15.9 years	-
Mean wall thickness of gallbladder (Mean ± SD)	5.1±1.3 mm	-
Clinico- radiological/pathological features of the IGBC cases (n=09)		
Clinico-radiological diagnosis		
• Chronic cholecystitis + cholelithiasis	08	88.9%
• Chronic cholecystitis	01	11.1%
Pathological Stage		
• T1a	03	33.3%
• T1b	03	33.3%
• T2	02	22.2%
• T3	01	11.1%
AJCC stage		
• I	05	55.6%
• II	02	22.2%
• III	02	22.2%
Type of the carcinoma		
• Adenocarcinoma	05	55.6%
• Mucin secreting adenocarcinoma	03	33.3%
• Papillary adenocarcinoma	01	11.1%

AJCC: American Joint Committee on Cancer; IGBC: Incidental gall bladder carcinoma; SD: standard deviation

DISCUSSION

IGBC is defined as cancer discovered at the time of histopathological examination of the specimen after cholecystectomy done for benign gallbladder disease without clinico-radiological and intraoperative suspicion of malignancy. [8,18] When compared with primary GBC, IGBC has better prognosis, prolonged survival and is potentially curable, provided timely detection and

adaptation of adequate surgical strategy is ensured. [17-19] As the clinical manifestation of IGBC may mimic various benign gallbladder diseases, the differential diagnosis is difficult and IGBC oftenly presents as a surprise to the pathologists. [17] However, the same can be easily missed in absence of the routine histopathological examination of the resected specimens. Hence, in order to increase the detection rate of occult

early-stage IGBC in benign gallbladder diseases, routine histopathological examination of every cholecystectomy specimen seems to be imperative.

The incidence of IGBC in benign gallbladder disease have been reported to range from 0.2% to 3.3% and may vary from one geographical location to another or among the different ethnicities, reason being the different lifestyles, cultural practices and the dietary factors. [8,10,18,21-26] In our study, the incidence of IGBC was found to be 1.2%, a finding which was in concordance with previous studies from India [22,27] and Nepal [23,24] wherein the IGBC incidence have been reported to range between 1.2% to 1.9%. However, in contrast to our study findings, various other studies from United Kingdom and North India have reported a much lower incidence of 0.1% to 0.77%. [8-10] With a male: female ratio of 1:1.3, a slight female preponderance and a mean age of 63.9±15.9 was noted among the patients with IGBC and these findings were in consonance with the previous studies. [8,9,11,28,29] IGBC is more likely to be found in elderly patients particularly when age is >60 years. [30] The female predominance can be attributed to the female hormone estrogen, which increases cholesterol saturation in bile thereby increasing the possibility of cholelithiasis; a major risk factor for GBC. [9] In the current study, cholelithiasis and chronic cholecystitis was associated with 88.9% cases of IGBC. Similar observation were reported in previous studies by Yadav *et al.* [27] and Gulwani *et al.* [5] who found cholelithiasis being associated in 93.7% and 95.6% cases of IGBC respectively. Chronic cholecystitis is characterized by marked thickening of the gall bladder wall with associated calcifications; eventually culminating in pathology termed the porcelain gallbladder. The presence of porcelain gallbladder is an established risk factor for the development of GBC. [31]

Normal thickness of the gallbladder wall is 1-2mm and if the thickness is >3mm it is considered as thickened gallbladder wall. [28] In the present study the mean wall thickness of gallbladder was 5.1±1.3 mm and all the IGBC cases, preoperatively diagnosed as cholelithiasis and chronic cholecystitis, had thickened gall bladder wall. Although thickening of gallbladder wall is seen in GBC but it is a non-specific finding and may also be associated with various gallbladder diseases like acute and chronic cholecystitis, cholelithiasis, cholesterosis and malignancies. [29] Hence, it is almost impossible to diagnose occult GBC or IGBC on radiological and macroscopic examination particularly on the basis of gallbladder thickness. [28,32,33] Also, a macroscopic absence of remarkable features does not preclude the presence of underlying premalignant or malignant lesions. [31] The aforementioned factors further substantiate the need of routine microscopic histopathological examination of all the resected gallbladder specimens after cholecystectomy. Previous literature from various studies also underlines the importance of routine histopathological examination of all the resected gall bladder specimens and considers it as the safest approach to minimize the chances of missing out IGBC cases. [18,19,25] Moreover in countries or subcontinents with

high incidence of GBC like India, Nepal, Pakistan, routine histopathological examination of all cholecystectomy specimens seems prudent.

The treatment and prognosis of GBC depends on the pathological stage and hence the timely and accurate diagnosis ensures better patient outcome. Primary GBC is usually detected in advanced stages and has a poor prognosis, however, IGBC is usually detected early and carries a good prognosis. [18,23,24,28] In our study, most of the patients (88.9%) were in early and surgically resectable stages, which has a better prognosis. Lymph node metastasis in GBC is also considered to be one of the most important prognostic factors [34], however as lymph node dissection is seldom carried out in benign gall bladder disease, the lymph node evaluation was not carried out in the current study.

CONCLUSION

IGBC although occult but is a catastrophic malignancy of the gallbladder and in most cases is primarily diagnosed for the first time by the pathologists while performing a routine histopathological examination of benign gallbladder specimens. The incidence of IGBC at our tertiary care center was found to be 1.2%. Despite thorough clinical and radiological examination, cases of IGBC tend to get missed particularly if selective histopathological examination of the resected gallbladder specimens is practiced. We recommend that routine microscopic histopathological examination of all the benign gallbladder specimens should be performed specially after cholecystectomy in high incidence areas. We realize that the data presented in this study have been taken from a single institution with a limited number of cases, and may not be representative of the whole Indian scenario or the correct magnitude of the disease. However, our study findings clearly underline the importance of routine histopathological examination of all the resected gallbladder specimens from benign gallbladder disease. A multidimensional approach with close clinical liaison between the Department of Surgery, Gastroenterology, Radiology and Pathology, will surely be helpful in early diagnosis and better patient outcome.

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Conflict of Interest: Nil

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