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Incidental gallbladder carcinoma in routine cholecystectomy specimens at tertiary care hospital

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ABSTRACT

Background: Incidental gallbladder carcinoma (IGBC) refers to gallbladder cancer which is not suspected clinically or radiologically and is detected for the first time on histopathological examination (HPE). **Aims and Objectives:** To find the incidence of IGBC and determine the pathological staging of IGBC accurately as it decides the mode of surgical intervention and thereby increases the quality of life. **Materials and Methods:** Three years of retrospective study were done from January 2020 to December 2022 at Sheth L. G. General Hospital. Routine histopathological evaluation of 857 such gallbladder specimens was carried out. Fifteen IGBC cases were reported whose pathological staging was done according to American Joint Committee on Cancer and were further analyzed in terms of demographic status, grading, lymph node status, margins, perineural, and lymphovascular invasion. **Results:** IGBC incidence was 1.75%. Out of 15 IGBC cases, 73% were females. Cholelithiasis was present in 86% of such cases. Gross inspection of all the IGBC-reported specimens revealed thickened gallbladder wall. All cases were adenocarcinoma – pancreaticobiliary type and the most common histologic grade reported was G2. Tumor cells invading the muscularis propria were observed in 7 cases (pT1b), and peri-muscular connective tissue in 7 cases (pT2). Tumor cells invading the serosa were seen in 1 case. (pT3). **Conclusion:** It is crucial to correctly report the pathologic T stage which determines patient's survival. The differentiation between pathologic stage pT1a and pT1b should be made cautiously, as this decides the surgical mode of intervention required for increasing the quality of life. In our study, we found the incidence of IGBC to be 1.75%. HPE of all routine cholecystectomy specimens is the gold standard for IGBC detection and is highly recommended irrespective of the radiological diagnosis or macroscopic findings.

Key words: Cholecystitis; Gallbladder neoplasms; Incidental; Histopathology

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INTRODUCTION

Gallbladder carcinoma (GBC) is the most frequently encountered cancer of the biliary tract globally and accounts to be the 5th most common cancer of the gastrointestinal tract.[1] In India, gallbladder carcinoma is the most common cancer of the gastrointestinal tract.[2] The clinical manifestations of GBC are usually identical to those associated with cholecystitis or cholelithiasis. Approximately, 90% of GB (gall bladder) carcinomas have associated stones.[3] It is difficult to differentiate early stage of GBC from chronic cholecystitis because it is asymptomatic.[4] Its incidence is high in South America and Asia, where there are high rates of cholecystitis and salmonella infection, both of which are reported as risk factors for GBC.[5-7] Polyps especially those which are more than 1 cm have an increased risk of progressing into neoplasm.[8,9] The prognosis of GBC is poor, which is due to a low early diagnosis rate and poor biological behavior where the 5-year survival rate of GBC is <5%.[10-12]

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Incidental GBC (IGBC) refers to GBC which is not suspected clinically or radiologically and is detected for the first time on histopathological examination (HPE). Studies in literature have reported IGBC from 0.3% to 1.5%.[13] IGBC has a better prognosis and improved quality of life as it is detected on HPE at an early stage and radical cholecystectomy is the standard treatment for IGBC. Hence, it has been the routine practice to submit all cholecystectomy specimens to HPE to exclude GBC.[14]

In IGBC, the pT stage is the most crucial factor in deciding the mode of surgical intervention. Simple cholecystectomy suffices for pT1a invasion depth. For patients with pT1b and greater depth of invasion, extended hepatic resection and regional lymphadenectomy are advised because it increases survival.[15] The main aim of the study is accurately determining the pathological staging of IGBC as it decides the mode of surgical intervention and thereby increases the quality of life.

AIMS AND OBJECTIVES

To find the incidence of gallbladder cancer among patients undergoing cholecystectomy due to benign gall bladder disease and to determine pathological tumour staging of IGBC.

MATERIALS AND METHODS

A retrospective analysis of all the patients who underwent open or laparoscopic cholecystectomies with a clinical-radiological diagnosis of benign gallbladder disease at LG Hospital Maninagar during the period from January 2020 to December 2022 was performed. The patients with clinically or radiologically suspected gallbladder malignancies were excluded from the study. A total of 857 cholecystectomy specimens with a clinico-radiological diagnosis of benign gallbladder diseases were received, out of which 14 were histologically confirmed as gallbladder malignancies. All these cases were of IGBCs since there was no preoperative suspicion of malignancy either clinically or radiologically in each of them. IGBC diagnosis was confirmed on hematoxylin and eosin-stained, formalin-fixed, paraffin-embedded sections. The gallbladder wall was considered thickened if it was found to be >3 mm on radiological imaging or HPE. The normal thickness of the gallbladder wall is reported to be 1–2 mm. The pathological staging of carcinoma was determined according to American Joint Committee on Cancer gallbladder cancer staging System 8th Edition. Information regarding age, sex, and presenting complaints was extracted from the histopathology laboratory forms. The clinical manifestations, preoperative radiological investigations, and histological features were analyzed and the results were evaluated.

RESULTS

A total of 857 cases of cholecystectomy specimens without any preoperative suspicion of malignancy were received in the department over a period of 2 years. The mean age at the time of surgery was 43 years (range 6–92 years). There were 176 (20.5%) males and 681 (79.5%) females with a male:female ratio of 1:3.8. The most common manifestation was pain in the right hypochondriac region seen in 88% of the patients followed by nausea and vomiting (7%) and epigastric pain (5%). Chronic calculous cholecystitis was the most occurring disease seen in 692 patients (80.7%) followed by chronic acalculous cholecystitis in 88 patients (10.37%). Xanthogranulomatous cholecystitis was seen in 06 (0.7%) patients, while 03 (0.3%) cases of adenomyomatosis and 02 (0.2%) cases of mucocele were reported. Chronic cholecystitis with low-grade dysplasia and those with high-grade dysplasia were reported in 9 (1.05%) and 2 (0.23%) cases respectively (Table 1). Fifteen cases (1.75%) were diagnosed as IGBC (Table 2). It was noted that out of these 15 cases of IGBC, 11 (73%) were female patients and 4 (27%) were male. The mean age group of affected patients was 55.47 years. Gross inspection of all 15 IGBC-reported specimens revealed thickening of the gallbladder wall (Figure 1a). The mean gallbladder wall thickness in IGBC reported patients was 1±0.78 cm (Table 3). Cholelithiasis was present in 13 (86%) cases of IGBC (Table 4). There was a significant association between age and pathological stages pT1b, pT2a, pT2b, and pT3 (Table 5). Tumor cells invading the muscularis propria were observed in 7 cases (pT1b) (Figure 1b), and peri-muscular connective tissue in 7 cases (pT2). Tumor cells invading the serosa were seen in 1 case. (pT3). There were no cases of IGBC with pathological stage T1a (Table 6). On microscopic examination, all IGBC cases showed features of adenocarcinoma – pancreatobiliary type. Histologic grade G2 was seen in 12 (80%)cases of IGBC whereas grade G1 and G3 were seen in 2 and 1 cases each of total IGBC cases. Lymphovascular invasion and perineural infiltration were seen in 2 cases and 6 cases, respectively. Histologically, surgical margins were positive in only 1 case (7%) of total IGBC cases. Two out of 15 (13%) IGBC cases showed positive lymph node status (Table 7).

DISCUSSION

The early-stage gallbladder cancer is generally diagnosed incidentally because of the symptoms overlapping with coexistent cholecystitis or cholelithiasis. The characteristics such as thickened gallbladder wall, gallbladder or CBD stones, a gallbladder mass and a pericholecystic collection are not hallmarks of GBC and they can be present in cholecystitis.

Table 1: Histopathological diagnosis of cases

Diagnosis	Number of cases (%)
Chronic calculous cholecystitis	692 (80.7)
Chronic acalculous cholecystitis	88 (10.37)
Chronic cholecystitis with low-grade flat dysplasia	9 (1.05)
Chronic cholecystitis with high-grade flat dysplasia	2 (0.23)
Acute calculous cholecystitis	6 (0.7)
Acute acalculous cholecystitis	34 (4)
Xanthogranulomatous cholecystitis	6 (0.7)
Adenomyomatosis	3 (0.3)
Mucocele	2 (0.2)
IGBC	15 (1.75)
Total	857 (100)

IGBC: Incidental gallbladder carcinoma

Table 2: Incidence of incidental gall bladder carcinoma

Findings	n (%)
Benign gallbladder	842
IGBC	15 (1.75)

IGBC: Incidental gall bladder carcinoma

Table 3: Distribution of incidental gallbladder carcinoma cases according to sex, age, and wall thickness

Variable	Value
Sex, n (%)	
Male	4 (27)
Female	11 (73)
Age (mean±SD)	55.47±14.61
Mean wall thickness (mean±SD)	1±0.78

SD: Standard deviation

Table 4: Incidental gallbladder carcinoma-calculous or acalculous

IGBC	n (%)
Calculous	13 (86)
Acalculous	2 (14)

IGBC: Incidental gall bladder carcinoma

Gallbladder carcinomas are epithelial in origin and they constitute about 98% of all the gallbladder malignancies. Among these, adenocarcinomas comprise 90% of all the GBCs. Most of these adenocarcinomas (70%) are diffusely infiltrating, while the remaining (30%) reveal intraluminal polypoid growth.[16] The infiltrating carcinomas grossly appear as focal or diffuse areas of thickening, nodularity, or induration in the gallbladder wall due to their submucosal extension. On gross examination, diffuse thickening of gallbladder wall was observed in all 15 cases of IGBC (Figure 1a) in this series and none of them revealed any intraluminal growth or mass lesion.

Table 5: Association of age with pathological stages

Stage	n	Age (years), mean±SD	Correlation	P
T1a	0	-	-	-
T1b	7	43.00±8.04	−0.82	<0.05
T2a	5	60.80±4.27	0.26	<0.05
T2b	2	72.50±3.54	0.47	<0.05
T3	1	82.00±-	0.50	<0.05

SD: Standard deviation

Table 6: Pathological staging of 15 incidental gallbladder carcinoma cases

Diagnosis	Status	n (%)
Pathological stage	T1a	0
	T1b	7 (47)
	T2a	5 (33)
	T2b	2 (13)
	T3	1 (7)

Table 7: Histopathological features of 15 incidental gallbladder carcinoma cases

Variable	n (%)
Tumor type	
Adenocarcinoma-pancreaticobiliary type	15 (100)
Histologic grade	
1	2 (13)
2	12 (80)
3	1 (7)
Lymphovascular invasion	
Present	2 (13)
Absent	13 (87)
Perineural invasion	
Present	6 (40)
Absent	9 (60)
Surgical margin status	
Positive	1 (7)
Negative	14 (9)
Lymph node status	
Positive	2 (13)
Negative	13 (87)
Depth of invasion	
pT1b	7 (47)
pT2	7 (47)
pT3	1 (6)

Histologically, all the 15 cases in this series were adenocarcinomas – pancreaticobiliary type, with 7 cases in pT1b (Figure 1b), 5 cases in pT2a, 2 cases in pT2b, and 1 case in pT3. The pathological staging was recognized as an important prognostic factor.

The gallbladder wall's normal thickness is 1–2 mm. Grossly, if the thickness of the gallbladder wall is >3 mm, then it is called thickened gallbladder wall.[17] The gallbladder wall thickening is a nonspecific finding that may be associated with a spectrum of gallbladder diseases like acute cholecystitis, chronic cholecystitis, cholelithiasis, and

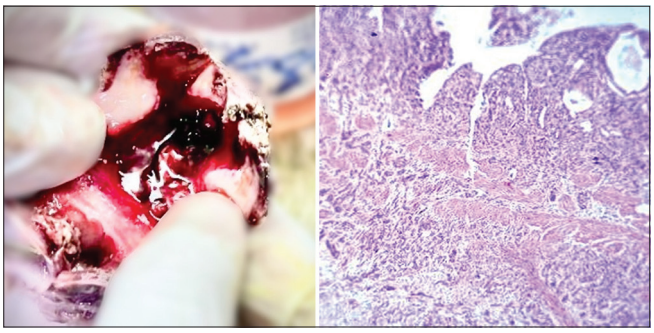

Figure 1: (a) Incidental gallbladder carcinoma case – Gross image showing thickened gallbladder wall and (b) microscopic image depicting tumor cells infiltrating muscularis propria – pT1b

Table 8: List of various studies showing the incidence of incidental gallbladder carcinoma

Study	Incidence (%)	Number of cases studied
Khoo et al.[21]	0.62	1122
Ghimire et al.[22]	1.28	783
Kalita et al.[23]	0.44	4115
Shah and Degloorkar[4]	0.87	803
Our study	1.75	857

malignancies.[18] Hence, occult carcinoma gallbladder or IGBC is almost impractical to be diagnosed solely upon radiological and macroscopic examination, especially on the basis of gallbladder wall thickness.[19] The only way to diagnose IGBC is a microscopic HPE.[20] In our study, the mean wall thickness of the gallbladder was 1±0.78 cm, and in all the IGBC cases which were preoperatively diagnosed as cases of benign gallbladder diseases by radiologists and surgeons, the gallbladder wall was found to be thickened on HPE. Flat dysplasia is graded as low- or high-grade. Since there is an association between flat dysplasia and invasive carcinoma, extensive further sectioning of the gallbladder is needed when dysplasia is reported on initial sections to rule out any adjoining adenocarcinoma.[16] 11 cases were reported as flat dysplasia whose further extensive sectioning revealed no adjacent adenocarcinoma.

The current study highlights the fact that it is not easy to suspect malignancy in gallbladder specimens based on clinico-radiological examination. We propose that all the benign gallbladder specimens should be routinely submitted to the histopathology lab for examination after cholecystectomy to exclude IGBC. Furthermore, if IGBC is detected, pathological staging is a significant prognostic factor.

The incidence of IGBC in our study was 1.75% which is relatively higher as compared to other studies listed in Table 8.

Limitations of the study

Since the study was conducted at a single centre, the incidence of IGBC in this study may not accurately represent the incidence in the population.

CONCLUSION

Proper staging and histopathological evaluation are indispensable in guiding the surgeon's operation. It is important to correctly assign the T stage, the most significant variable on patient survival and residual recurrences. The differentiation between pathologic stage pT1a and pT1b should be made cautiously, as this decides the surgical mode of intervention required for increasing the quality of life.

Gallbladder cancers are one of the common tumors of gastrointestinal tracts and are known to have a poor prognosis. In our study, we found the incidence of IGBC to be 1.75%. Histopathological evaluation of all the routine cholecystectomy specimens is the gold standard for IGBC detection and is highly recommended irrespective of the radiological diagnosis or macroscopic findings.

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Authors Contribution:
KJM- Definition of intellectual content, literature survey, prepared first draft of manuscript, data collection, data analysis, manuscript preparation and submission of article; **SKP-** Design of study, implementation of study protocol, statistical analysis and interpretation, manuscript editing and review manuscript and manuscript submission; **KHP-** Concept, design, clinical protocol, manuscript preparation, editing and submission; **MNL-** Literature survey, manuscript editing and preparation of figures; **RPM-** Coordination and manuscript revision.

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