Incidental gallbladder carcinoma: value of routine histological examination of cholecystectomy specimens

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ABSTRACT

Cholecystectomized specimens are one of the frequently encountered specimens in daily routine histopathological work in the pathology department. With the expectation that most of the gallbladder specimens harbor benign disease, it is at times surprising to find occult malignancy. This study aims to find out the frequency of primary gallbladder carcinoma and incidental primary carcinoma, detected during routine histological examination of gallbladder specimen that were submitted in pathology department of Nepal Medical College Teaching Hospital (NMCTH) as well as to assess the need of histopathological examination of cholecystectomy specimens. Retrospective study was done in total 668 cases of cholecystectomies specimens submitted in NMCTH histopathology department during 5 yrs of duration from Jan 2003 to Dec 2007. There were total 22 cases of primary gallbladder carcinoma and 2 cases of metastatic cholangiocarcinoma in gallbladder. The incidence rate of primary malignancy was 3.3% and was commonly found in female at 7th decade of their life. Adenocarcinomas were the most common histological type with poor differentiation and diagnosed frequently at stage IIA. The rate of incidental primary carcinoma of gallbladder was 1.4%, detected commonly at stage I. Combined preoperative and intraoperatively, only 55.0% of histologically proven gallbladder malignancies were correctly identified. Intraoperative findings of incidental carcinomas included thickened GB (3 cases), distended GB (2 cases), GB polyp (1 case) and no obvious abnormality were mentioned in 3 cases. Therefore, every cholecystectomy specimen should be examined histopathologically to detect possible incidental carcinomas.

Keywords: Cholecystectomy, incidental carcinoma, histopathology.

INTRODUCTION

Cholecystectomy is one of the most common abdominal surgeries. In the U.S, annual incidence of gallbladder diseases is estimated about one million and among them approximately 500,000-600,000 undergo surgery.[1] Gallbladder malignancy is a lethal disease and is the fifth commonest malignancy in the gastrointestinal tract.[2] Clinical presentation of gallbladder malignancy and benign gallbladder disease is almost similar and most of the times it is masked by chronic cholecystitis.[3] Preoperative diagnosis of carcinoma of gallbladder is the exception rather than the rule, occurring in fewer than 20.0% of patients.[4] Hence, It is likely for finding gallbladder tumours incidentally during surgery done for stones or biliary tract diseases.[1] Incidental carcinoma of gallbladder includes incidental finding of carcinoma in histopathological examination of gallbladder specimen sent after cholecystectomy performed for benign gallbladder disease or removed during other abdominal surgeries.

Our study aims to establish the frequency of primary carcinoma of gallbladder and incidental carcinoma in routine cholecystectomy specimen. Further, we would like to assess whether routine histological examination of every cholecystectomised specimen is justifiable or not.

MATERIALS AND METHODS

We retrospectively reviewed histopathological records of total 668 patients who underwent cholecystectomy for hepatobiliary disease or for other diseases requiring laparatomy conducted in NMCTH during a period of 5 years from January 2003 to January 2007. Gross findings and histological diagnosis, based on routine examination of H and E stained slides, were noted from histopathology record book. Clinical records regarding clinical presentation, investigation mainly USG finding, preoperative diagnosis and intraoperative findings were retrieved from computer record databases. AJCC tumour staging system based on TNM (tumour, node, metastasis) classification was used for the staging of the gallbladder carcinoma.

Statistical analysis was done using SPSS 10 analyzer.

Table-1: Histological types of gallbladder neoplasm

Histological types of GB tumour	**No. of cases**
Benign	
Tubular adenoma of pyloric type	1
Malignant Primary	
Well differentiated adenocarcinoma	2
Moderately differentiated adenocarcinoma	5
Poorly differentiated adenocarcinoma	10
Papillary adenocarcinoma	4
Sarcoma	1
Secondary	
Metastatic cholangiocarcinoma	2
Total	25

RESULTS

Total 668 cholecystectomies were performed during 5 yrs period. The age of patients with gallbladder disease ranged from 7yrs to 89yrs and were most commonly found in the 3rd decade (164/668 cases,24.6%). There were 173 males and 495 females with M: F ratio of 1:3. Out of 668 cases, 643 were nonneoplastic gallbladder disease and 25 were neoplastic lesions of gallbladder. The age of patients with malignancy varied from 30yrs to 80 yrs with highest peak in the 7th decade. Mean age for malignancy was 56.25 yrs. Mean age for malignancy for males was 65 yrs and 53.94yrs for females. Malignancy was also more frequently encountered in females (19/ 24, 79.2%).

Benign gall bladder diseases were mainly chronic cholecystitis, frequently in association with adenomyosis and cholesterosis. Others in minority included chronic cholecystitis with acute exacerbation, follicular cholecystitis, eosinophilic cholecystitis, xanthogranulomatous cholecystitis, porcelain gallbladder, empyema gangrenous cholecystitis, tuberculosis, acute cholecystitis and xanthomatous polyp.

Out of 25 neoplastic lesions, there was only one benign neoplasm, i.e. a case of gallbladder adenoma of pyloric type and the rest were malignant (22 primary gallbladder malignancies and 2 metastatic carcinoma of cholangial origin) as shown in Table-1. The frequency of the latter is 3.3% of all gallbladder disease. All primary malignant lesions (21/22, 95.4%) were adenocarcinomas except one which was a sarcoma. Most of the adenocarcinomas were poorly differentiated (11/21, 52.38%). At the time of diagnosis, slightly more than 1/3rd of primary carcinoma of gall bladder (8/21, 38.1%) were at TNM stage pT3. Metastasis was more commonly seen in liver (4 cases of primary carcinoma of gallbladder). Other organ involved were pancreas (2 cases), duodenum, colon and omentum (1 case) and ovary (1 case). One of the metastatic carcinoma of gallbladder was at stage IV with positive ascitic fluid for malignancy.

Clinicopathological analysis could be performed in only 570 cases out of the total 668 cases, due to the lack of complete clinical records in the rest. According to the clinical records, cholecystectomies were performed for symptomatic benign gallbladder disease, clinically suspicious malignancy of gallbladder or malignancy elsewhere and laparatomy done for non- biliary tract diseases. Out of which 550 cholecystectomy specimens were of benign type and the remaining 20 cases had malignancy which was proven by histological examination.

Gallstones were present in both benign and malignant cases with frequency of 91.0% (503/550 cases) and 80.0% (16/20 cases) respectively.

Clinical presentation of histopathologically proven benign and malignant gallbladder diseases was similar. Pain in the right upper quadrant with or without nausea and vomiting, fever, jaundice or palpable gallbladder mass was the common signs and symptoms. Frequency of common clinical presentation in histologically proven malignant cases is shown in Table-2. There were 32 asymptomatic patients undergoing cholecystectomy and all of them had benign inflammatory gallbladder disease. These included elective cholecystectomy performed for gallstones found incidentally by USG (22 cases) and incidental cholecystectomy done for asymptomatic gallstones during other abdominal operative procedures.

Of 20 proven malignant cases, preoperative diagnosis of malignancy was suspected only in 6 cases. Intraoperatively, obvious growth was observed in 10 cases, raising high index of clinical suspicion of malignancy. However, later one was found out to be a benign inflammatory disease diagnosed as follicular cholecystitis. Though, peroperative findings were

Table-2: Common clinical presentation of gallbladder cancers

Clinical presentation	No. of cases
Pain right upper quadrant	15
Jaundice	2
Pain with palpable mass	2
Pain with jaundice	1
Total	20

Table-3: Clinical and histopathological findings of incidental GBC

Case	I.P.no	Year of diagnosis	Age	Sex	Clinical diagnosis	Intraoperative findings	Gross features	Histological diagnosis	Turnover stage(pT)
1	154453	2004	38	F	AC, calculous	No susp lesion	Fungating mass	WDA	pT1a
2	207172	2006	70	F	AC, calculous	No susp lesion	Irregular mucosa	MDA	pT1b
3	210846	2006	58	M	Obstructive jaundice with mirizzi syndrome	Thickened wall	Contracted GB	PDA	pT1b
4	222876	2007	62	F	CC with CBD stone	No susp lesion	Thick fibrosed wall	PDA	pT2
5	192549	2007	55	F	Ca HOP	Ca HOP; dilated GB	Granular mucosa	PDA	pT3
6	235847	2007	47	F	GB polyp	GB polyp	Solid G/W mass	Pap Ca	pT1a
7	171669	2005	68	F	CC, calculous	Thickened wall	Solid G/W mass	Pap Ca	pT1b
8	229827	2007	53	M	CC	Periampullary carcinoma; dilated GB	Fungating mass	Pap Ca	pT3
9	110077	2003	31	F	CC, calculous	Thickened wall	Solid G/W mass in thickened wall	Metastatic cholangi ocarcinoma	pT3

Note: AC- Acute cholecystitis; CC- Chronic cholecystitis; CBD- common bile duct; GB- gallbladder; GBC- Gallbladder carcinoma; Ca HOP- carcinoma head of pancreas; Susp- suspicious; G/W- grey white; WDA- well differentiated adenocarcinoma, MDA- moderately differentiated adenocarcinoma; PDA- poorly differentiated adenocarcinoma

missing in 2 histologically proven malignant cases, USG findings in these two cases were GB masss and? liver metastasis/? HCC respectively. Therefore, total 11 cases had clinical suspicion of malignancies with both combined preoperative and postoperative findings. Remaining 9 cases of malignancies were incidentally found by histological examination of gallbladders that were removed for benign gallbladder disease or simultaneously removed during laparatomy performed for suspected malignancy of other organs such as pancreas and periampullary region. However, suspicious growth was observed during grossing in 5 cases out of 9 incidentally found carcinomas. None of the gallbladder described unremarkable had occult carcinoma microscopically. Clinical details, peroperative findings, gross features, histological diagnosis and the stage at presentation of these incidentally found carcinomas are given in Table-3.

Thus, the frequency of incidental primary gallbladder carcinoma was 1.4% (i.e. 8/570 cases). One of the metastatic cholangiocarcinoma was also detected incidentally accounting to 0.17% of incidence rate of secondary malignancy in gallbladder. Out of 9 incidental carcinomas, stones were present in 6 cases (66.6%). Clinical outcome of the patients with malignancies after cholecystectomy could not be retrieved as most of them were lost to follow up.

DISCUSSION

Gallbladder malignancy is a rare entity, however, is common in the gastrointestinal tract. Most are diagnosed at advanced stage with dismal prognosis having 5 years survival rate of less than 5.0%.[5] Detection at early stage has excellent prognosis increasing up to 90.0-100.0% 5 years survival rate.[6] However, early detection is not possible due to delayed onset of symptoms or is masked off by chronic cholecystitis, and is usually detected during simple cholecystectomy as incidental finding.

Our study revealed the incidence rate of primary gallbladder malignancy to be 3.3%. Different international studies[3,7,8] have reported different incidences ranging from 0.17% to 12.4%. Pradhan *et al*,[9] showed incidence rate of 2.6% for primary gallbladder malignancy in Nepal. Difference in incidence rate among various studies might be due to exclusion of inoperable GB malignancy in some and variation in prevalence of gallstone disease in different ethnic group, race and regions.

GB malignancies were commonly seen in 7th decade of life with mean age at presentation being 56.25yrs and more commonly encountered in females (79.2%). Similar findings were encountered in studies by Ataur *et al*,[3] Hsieh *et al*[8] and Tantia *et al*.[10] The higher incidence of overall gallbladder disease in females (three times more in our study) explains the more frequent occurrence

Table-4: Comparison of Incidence rates in different studies

Studies	No. of IGBC cases	Total no. of Cholecystectomized cases	Incidence rates
Daphna *et al*[11]	6	1697	0.3%
Tantia *et al*[10]	19	3205	0.6%
Mittal *et al*[17]	13	1305	0.9%
*Morera *et al*[13]	4	372	1.1%
*Amanullah *et al*[12]	8	428	1.9%
Shigeki *et al*[14]	4	84	4.7%
*Present study	9	570	1.4%

IGBC- Incidental gallbladder cancer

*Incidence rates in the studies with bold letters are similar to that of the present study

of GB malignancy in them. In contrast to benign diseases, malignancies were found to increase with increasing age.

Gallstones were associated in 80.0% of GB malignancies. Cholelithiasis is a well-established risk factor for the development of gallbladder carcinoma. According to Daphna *et al*,[11] gallstones are present in 70.0-92.0% of affected patients. Gallstones cause chronic irritation and inflammation of the gallbladder, which leads to mucosal dysplasia and subsequent carcinoma that takes a long duration for promotion of tumour proliferation and hence the occurrence of malignancy in the elderly age group.

Among primary malignant lesions all were adenocarcinomas except one which was primary sarcoma. Adenocarcinoma was seen more frequently in other studies as well viz. 100.0%, 90.0% according to Amanullah *et al*[12] and Daphna *et al*[11] respectively.

Majority of malignant cases were diagnosed at advanced stage with poor differentiation. Maximum number, i.e. 8/20 cases were at TNM stage T3. Liver was the commonest site of spread. Diagnosis at advanced stage thus is the reason for the high morbidity and mortality for GB malignancies.

The present study showed the frequency of the primary incidental carcinoma to be 1.4%. Amanullah et al[12] and Morera *et al*[13] found occult gallbladder cancer incidence of 1.9% and 1.1% respectively which are closer to our observation whereas it was less i.e. 0.3% in the series according to Daphna *et al*.[11]It was even higher, as shown by Shigeki *et al*,[14] finding incidence of incidental GBC to be 4.7%. Wide range of incidence in different studies, as shown in Table-4, might be due to difference in total number of study population of cholecystectomy cases carried out for the study purpose. Incidence of primary GBC itself is low and finding of incidental carcinoma would be low too. Thus, the studies with very high denominator (number of study population) would show very low incidence in comparison to low denominator with similar number of incidental carcinomas. All the Incidental carcinomas were found in symptomatic patients and all were histologically diagnosed as adenocarcinoma graded well to poor differentiation and of papillary type. Other studies showed incidental carcinoma even in asymptomatic patients. [12] Most of the primary incidental carcinomas (5/8 cases) were at early stage (T1a, T1b) and not a single case was found with distant metastasis. Tantia *et al*[10] and Vincenzo *et al*[15] also found the majority of incidental carcinomas at early stage.

There is an issue of debate regarding routine histopathological examination of gallbladder. Some authors[7,16,17] suggest more selective approach to histological examination of gallbladder specimen. Bazoua *et al*[7] observed that all cancer gallbladders had thickened fibrotic wall. Different studies[16-19] also showed similar observation that, abnormal macroscopic appearance were present either pre or intraoperatively in all cases of invasive carcinoma and thus recommended for selective policy rather than routine histological examination of nonfibrotic or thickened-wall gallbladder. However Samad *et al*[20] and Amanullah *et al*[12] suggested routine histological examination of all cholecystectomized specimens. Also, the report by working group of Royal college of Pathologists stated that gallbladder should be examined, as significant pathology may be present with normal gross morphology.[21]

Our observation showed that radiological and peroperative findings were not helpful in raising high index of suspicion in most of the cases of incidental carcinomas. Preoperative diagnosis of malignancy was difficult, missing 70.0% of carcinoma gallbladder. Combined preoperative and intraoperative findings failed to detect 45.0% of malignant cases in this study. Macroscopic findings of all incidental carcinomas had thick wall gallbladder in other studies.[6,11,19] However, our study showed thickened GB in only 3 cases of incidental carcinomas and the remaining 6 had no suspicious lesion or any specific changes intraoperatively. While on gross, other than thickened GB, nonspecific mucosal changes such as, irregular, granular mucosa, contracted GB were noted. Therefore no specific clinical or macroscopic finding can be assigned to characterize incidental carcinoma pre or intraoperatively to have clinical suspicion of malignancy. Only histological examination remains the tool for the detection of occult malignancy.

Authors who propose for selective policy of histological examination state that incidental carcinomas if found during histopathological examination would be at early stage and simple cholecystectomy performed for benign gallbladder disease would be sufficient enough in giving good clinical outcome.[7,19] In contrast to this statement, our study reveals not only early stage (T1a and T1b) incidental carcinomas but also, 2 cases at stage T2 and another 2 cases at stage T3. Incidental carcinoma of gallbladder at stage T2 or advanced stage, second radical operation is suggested by Eric *et al*.[5] Even for the management of early stage carcinoma, especially T1b, Vincenzo *et al*[15] suggested more aggressive surgery, as there was improvement of survival rate in comparison to those treated with simple choecystectomy. Similar view is shared by Mishra *et al*[6] recommending re-resection for all disease except Stage IA, for patients whose cancer is an incidental finding on pathologic review. However, there is still a controversy regarding management of GB malignancy at stage T1b.[5] Decision upon further surgical management of the incidental carcinomas thus depends upon the stage after pathological examination as well as, patient's fitness for re- surgery.

Routine histological examination of all gallbladder specimen is therefore well justified as finding of incidental carcinoma might alter the management and thus the clinical outcome.

The frequency of primary gallbladder carcinoma in our study was 3.29% with incidental primary carcinoma accounting to 1.4%. Most of the gallbladder carcinomas are missed during preoperative, ultrasound and intraoperative examination unless presented at advanced stages. Macroscopic abnormal findings simply cannot be relied on selecting gallbladder specimen for suspicion of malignancy, and even nonspecific macroscopic changes or intraoperatively normal looking gallbladder to surgeon's eye might harbor malignancy. For every incidentally found carcinoma, simple cholecystectomy may not be sufficient as some might be detected at locally advanced stage or at T1b requiring further aggressive surgery. Keeping in view of all these possibilities, we therefore recommend for routine histological examination of every cholecystectomized specimen regardless of macroscopic appearance of gallbladder.

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