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Incidental gallbladder carcinoma in laparoscopic cholecystectomy: Five years local experience

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Abstract

Background: Carcinoma of the gallbladder is the most common malignancy of the biliary tract. Most of the cases are diagnosed as an incidental case among patients undergoing cholecystectomy. The objectives of this study were to report the rate of incidental carcinoma of gallbladder in patients undergoing cholecystectomy and to study the demographic profile and prognosis of these patients in our locality.

Methods: A retrospective study was carried out in our general hospital during 2007-2012. The hospital records and histopathology reports of 1982 patients who had undergone elective laparoscopic cholecystectomy were studied.

Results: Out of 1982 cases of cholecystectomy, gallbladder cancer was detected in 10 (0.5%) cases and was more common in females (M:F ratio = 2:8) .The mean age of occurrence was 73.6 years. Most of the cases diagnosed, were at their early stages and only two of them were in pT3 pathological stage. Five of those patients survived to date with a mean follow up duration of 26 months.

Conclusion: The rate of incidental carcinoma of gallbladder is 0.5% in our locality and nearly half of patients were early stage with acceptable five year survival rates. Routine postoperative histopathology of gall bladder is mandatory. (El Med J 2:2; 2014)

Keywords: Gallbladder Carcinoma, Laparoscopic Cholecystectomy, Incidental

Introduction

Carcinoma of the gallbladder (GBC) is the fifth most common cancer of digestive tract and the most common malignancy of the biliary tract. It is an aggressive disease because symptoms and signs usually appear late and most patients are seen at an advanced stage (which is due to both the anatomic position of the gallbladder, and the vagueness and non-specificity of symptoms) with a poor prognosis [1, 2]. More than 80% of gallbladder cancers are adenocarcinomas [3]. The clinical manifestations of GBC are generally indistinguishable from those associated with cholecystitis or cholelithiasis. Around 90% of GBC have accompanying cholelithiasis [4]. Stones and chronic inflammation are the risk factors for GBC. However, only 0.5–3% of patients with cholelithiasis will actually develop GBC [5].

Cholecystectomy is the most common major abdominal procedure performed worldwide. This procedure is being performed at an increasing rate according to hospital records [6]. Reports from many regions of Saudi Arabia show a striking increase in occurrence of gallstones during the last two decades [7]. In the era of laparoscopic cholecystectomy (LC), despite advancements in various diagnostic procedures, preoperative diagnosis of GBC is an exception rather than the rule, occurring in fewer than 20% of patients [8]. The incidence of incidental GBC is 0.3-5% of all cholecystectomies. Incidental GBC has dramatically increased and is now the major way patients present with GBC. GBC not only presents a diagnostic dilemma but also poses a difficult treatment option in the era of laparoscopic cholecystectomy [9, 10].

In this single-center study, we report our experience with gallbladder cancer incidentally diagnosed during or after laparoscopic cholecystectomy performed for gallstone disease.

Patients and Methods

We evaluated the medical records of patients with gallstone disease who underwent LC in the Department of General Surgery of our General Hospital over the past five years. Routine preoperative assessment was performed in all patients, including liver function tests and abdominal ultrasonography. Exclusion criterion was existence of gallbladder polyps detected during preoperative ultrasonography. All operations were carried out by the authors using the standard four-port, two-hand technique [11}. Post-operatively all gall bladder specimens were sent for histopathological examination. Tumor staging was based on the 7th edition of the American Joint Committee on Cancer (AJCC) manual (Table 1) [12].

Recorded data included patients' demographics, details of operative procedures, perioperative outcomes, tumor histopathology, follow-up, and long-term survival. All the cases were further consulted with the oncologists for further adjunctive therapy and postoperative follow-up was done. Follow-up data were obtained for all patients through them. Statistical analysis was done using SPSS 19 software. The study was ethically approved by the ethical committee of our hospital.

Results

During the period from December 2007 to December 2012, we performed 1982 LC procedures. Nearly all patients had cholecystitis or cholelithiasis. Out of those cases, 10 cases were found to have GBC. Among them, eight were females and two were males, giving a male to female ratio of 1:4. These patients were between the ages of 56 and 91 years old. The mean age was 73.6 years (Table 2). Nausea, vomiting and pain in the right upper quadrant (RUQ) of the abdomen was the common clinical presentation in all the ten cases. Two patients presented with the features of acute cholecystitis, with a positive Murphy's sign. In the remaining patients, the symptoms were more chronic in nature and of a longer duration, which ranged from 6 months to 5 years. None of the ten cases were clinically suspected to have GBC preoperatively although all had preoperative routine ultrasound imaging (Figure 1).

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Table 1: TNM staging of gallbladder cancer [12]

Primary Tumor (T)	TX	Primary tumor cannot be assessed
	T0	No evidence of primary tumor
	Tis	Carcinoma in-situ
	T1	Tumor invades lamina propria or muscle layer
	T1a	Tumor invades lamina propria
	T1b	Tumor invades the muscle layer
	T2	Tumor invades the perimuscular connective tissue; no extension beyond the serosa or into the liver
	T3	Tumor perforates the serosa (visceral peritoneum) and/or directly invades the liver and/or one other adjacent organ or structure, such as the stomach, duodenum, colon, or pancreas, omentum or extra hepatic bile ducts
	T4	Tumor invades main portal vein or hepatic artery or invades multiple extra hepatic organs or structures
Regional Lymph Nodes (N)	NX	Regional lymph nodes cannot be assessed
	N0	No regional lymph node metastasis
	N1	Regional lymph node metastasis
Distance Metastasis	MX	Distant metastasis cannot be assessed
	M0	No distant metastasis
	M1	Distant metastasis

Figure 1: Pre-operative ultrasonographic picture of one case of GBC with thick walled gallbladder and multiple gall stones.

All cases had gallbladder stones. None of those patients were diagnosed for GBC preoperatively. Three cases needed conversion to open cholecystectomy and two of them were suspected during conversion, so extended cholecystectomy was done for both of them with excision of a wedge shaped area of the liver from the gallbladder bed (cleared later by histopathology [Figure 2]) with resection of visible and palpable lymph nodes.

Out of the 10 cases of incidental GBC, two patients died during hospitalization due to unrelated causes (acute myocardial infarction and massive cerebral hemorrhage). Two more cases died after 8 and 13 months of diagnosis due to causes unrelated to GBC. One patient died due to metastatic disease 3 months after surgery. Five patients (50%) have survived to date with a mean follow up duration of 26 months. The details of the 10 cases of incidental GBC has been described in (Table 2).

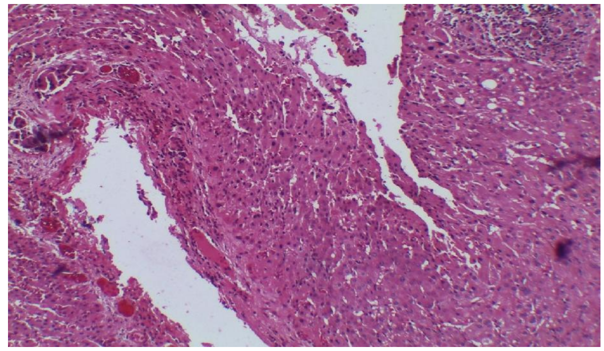

Figure 2: Attached hepato-parenchymal tissue. There is no tumor invasion.

Since, our hospital is a secondary care center, the cases were referred to an oncology center after histological diagnosis of malignancies for further treatment but we did establish contact with patients and relatives for estimation of the survival and mortality. The majority of the patients were in early pathological stages (pT1-3) and none was in pT4 stage (Figures 3-6).

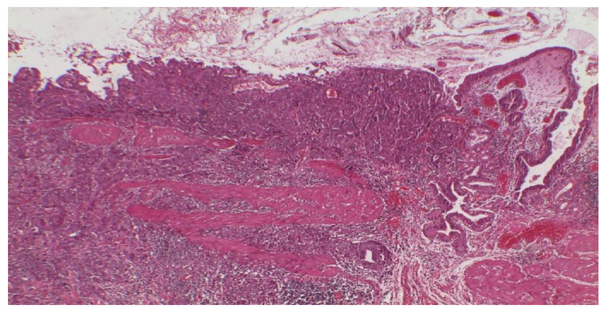

Figure 3: Intact mucosa is seen on the right. Abrupt area of tumor in which neoplastic structures invade the adventitia/serosa layer through the fragmented muscular layer.

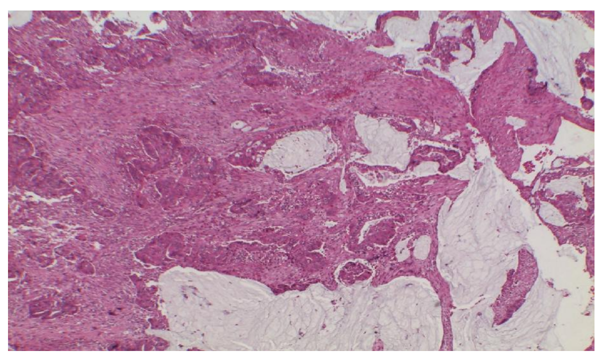

Figure 4: Mucinous adenocarcinoma with mucin secretion (mucin pools).

Figure 5: Gross picture of one case of GBC with diffuse wall thickening more in the neck and multiple gallstones.

Table 2: TNM staging of gallbladder cancer* [12]

Case	Age	Sex	Diagnosis (duration in years)	Ultrasound Findings	Operative Findings	Operation Type	Histological Diagnosis	Tumor Stage	Survival
1	91	F	CCC(4)	CCC,TW,GBD	LC No susp	SLC	WDA	pT2	Died
2	90	F	CCC(3)	CCC,TW,GBD	LC No susp	SLC	MDA	pT3	Died
3	74	F	CCC(1)	CCC,TW,GBD	OC Susp	C+LR+LN	PDA	pT2	Died
4	56	F	CCC(0.5)	CCC,TW,GBD	LC No susp	SLC	WDA	pT1a	Alive
5	62	F	CCC(4)	CCC,TW,GBD	LC No susp	SLC	WDA	pT1a	Alive
6	69	M	CCC(3)	CCC,TW,GBD	LC No susp	SLC	WDA	pT1b	Alive
7	77	M	A&CCC(5)	CCC,TW,GBD,PC	OC Susp	C+LR+LN	MDA	pT3	Died
8	83	F	CCC(7)	CCC,TW,GBD	LC No susp	SLC	WDA	pT1a	Alive
9	64	F	CCC(2)	CCC,TW,GBD,PC	OC No susp	SLC	PDA	pT1b	Died
10	70	F	CCC(3)	CCC,TW,GBD	LC No susp	SLC	WDA	pT1a	Alive

*A&CCC=Acute on top of chronic calcular cholecystitis; CCC=Chronic calcular cholecystitis; GBD=Gallbladder distended; Susp=Suspicious; TW=Thick wall gallbladder; PCF=Pericholecystic fluid; LC=Laparoscopic cholecystectomy; OC=Open cholecystectomy; SLC=Simple laparoscopic cholecystectomy; C+LR+LN=Cholecystectomy+localized liver resection+lymph nodes excision; WDA=Well differentiated adenocarcinoma; MDA=Moderately differentiated adenocarcinoma; PDA=Poorly differentiated adenocarcinoma

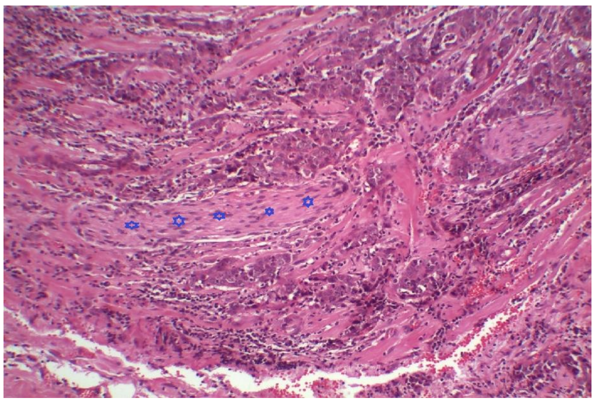

Figure 6: Perineural invasion (blue stars indicate nerve).

Discussion

Carcinoma of the gallbladder is a rare gastrointestinal malignancy. However, it is reported to be the most frequent carcinoma of the extra-hepatic biliary tract. Symptoms are non-specific and the diagnosis is often made at an advanced stage at operation for routine cholecystectomy. Thus, the outcome for GBC remains largely dismal [13].

We reported 7 cases of GBC out of 47 cases reported in Saudi Arabia during the period from 2007 to 2011 [14]. Our results agree with literatures in that GBC is two to six times more common in women than men. Incidence increases with age and more than 75% of patients with this malignancy are older than 65 years [15, 16]. Literature review revealed that 0.3% to 4.6% of the patients who underwent cholecystectomy for presumed benign disease were found to have GBC with more common incidence in eastern than western countries. The proportion of GBC detected in patients undergoing cholecystectomy for cholelithiasis in our study was 0.5% and is quite comparable with other literature (Table 3) [17-20]. In the present retrospective study, reviewing 10 patients with GBC surgical treatment remains the only treatment modality associated with a benefit in terms of survival. Simple cholecystectomy may be sufficient for patients with pT1a tumors by the TNM classification with cure rates ranging from 73 to 100%, even those diagnosed following LC [2].

Eight patients in our study had cholecystectomy alone as a definitive treatment for GBC, the lesion was (pT1a stage) in 4 patients, pT1b stage in two patients and pT2 in two more patients. For pT1b tumors (tumor invading the muscular layer) the benefit of radical resection is controversial. We performed simple cholecystectomy in those patients and later they were referred to oncologist for further treatment. No further surgery was required and no recurrence was noted during the follow up period. Some authors advocate radical resection on the basis of evidence of lymph node metastases in these patients as well as disease in gallbladder fossa. Thus, performing a lymphadenectomy with excision of at least a wedge of liver tissue from segments IV b and V may be indicated in pT1b Tumors [22].

The benefit of radical resection may be particularly pronounced among patients with muscle layer invasion as they have higher incidence of lymph node metastases. Excision of at least 2cm of liver tissue from the gallbladder fossa with lymphadenectomy were performed in two patients with tumor invading the muscle layer (pT3) proved by histologic examination of the cholecystectomy specimen. During recent years, extended operations combining a resection of the liver with wide lymph node dissection have improved the long-term survival [23, 24]. However, there are still many controversies regarding the type of surgical treatment for each stage of the disease [25].

The widespread use of laparoscopic techniques has led to an increase in referrals for cholecystectomy. As a consequence, the incidental finding of GBC at an earlier stage has altered the management and the outcome of the disease. However, GBC remains a lethal disease associated with a dismal prognosis. Controversies exist on the optimal treatment of this unexpected finding during routine laparoscopic cholecystectomy. The management is difficult because no guidelines have been established and some authors have reported worse overall prognosis when patients have not been adequately treated during the first operation. Simple cholecystectomy is generally considered as an adequate treatment for pT1b patients, but this is still a matter under discussion. Shirai has reported a favorable outcome regardless of the type of operation done (cholecystectomy alone or extended cholecystectomy) in early stages [13]. Advanced

Table 3: Comparison between other studies and our study

Author	Year	N	Cancer (%)	F/M ratio	Mean Age	pTis, pT1	pT2, pT3, pT4	Median Survival (months)
Sarli et al [33]	2000	2300	9 (0.39)	6/3	62.3	4	5	12
Daphna et al [17]	2002	1697	6 (0.35)	5/1	70	1	5	8
Antonakis et al [34]	2003	5539	11 (0.2)	8/3	57	0	11	8.1
Yamamoto et al [35]	2005	1663	9 (0.54)	4/5	73	4	5	19
Shimizu et al [36]	2006	1195	10 (0.84)	7/3	61.4	4	6	62.5
Amanullah et al [18]	2007	428	8 (1.9)	7/1	47	5	3	12
Yokomuro et al [20]	2007	84	4 (4.7)	2/2	75	2	2	NA
Kwon et al [38]	2008	1793	38 (2.12)	21/17	66	20	18	68
Tantia et al [16]	2009	3205	19 (0.59)	14/5	56	16	3	18.4
Choi et al [38]	2009	3145	33 (1.05)	24/9	63	12	21	46.3
Zhang et al [39]	2009	10466	20 (0.19)	16/4	65.7	8	12	43
Morera et al [19]	2009	372	6 (1.1)	2/4	63.8	2	4	23
Ghimire et al [40]	2011	783	10 (1.28)	7/3	63.8	8	2	8
Cavallaro et al [41]	2012	1490	19 (1.2)	11/8	68	7	12	38
Ioannidis et al [42]	2013	1536	14 (0.9)	11/3	69.4	5	9	NA
Our study	2013	1982	10 (0.5)	8/2	73.6	6	4	26

stage of the disease, because of delayed diagnosis, leads to its poor prognosis [26-30].

Gallbladder carcinomas are epithelial in origin and they account for 98% of all the gallbladder malignancies. Among these, adenocarcinomas account for 90% of all the carcinomas of the gallbladder [31]. In our series, all were adenocarcinoma and one had mucinous areas (Figure 4). The sub mucosal spread of the infiltrating carcinomas appears grossly as focal or diffuse areas of wall thickening, nodularity or induration in the gallbladder wall. Similar gross features were seen in all the 10 cases of incidental GBC in this series, and none of them showed any intraluminal growth or mass lesion (Figure 5).

In as many as 50% of cases, GBC are discovered at pathologic analysis after simple cholecystectomy for presumed gallstone disease. Five-year survival is 50% for patients with pT1 tumors. Patients with pT2 tumors have a 5-year survival rate of 29%, which appears to improve with more radical resection. Patients with lymph node metastases (pN1) or locally advanced tumors (PT4) rarely experience long-term survival. The site-specific prognostic factors include histologic type, histologic grade, and vascular invasion. Papillary carcinomas have the most favorable prognosis. Unfavorable histologic types include small cell carcinomas and undifferentiated carcinomas. Lymphatic and/or blood vessel invasion indicate a less favorable outcome. Histologic grade also correlates with outcome [12].

The importance of a histological examination of the post-cholecystectomy specimens cannot be over-emphasized. The non-specific clinical features and the sonographic findings of early GBC make the pre-operative diagnosis difficult and an incidental GBC has been recorded in every reported series of laparoscopic cholecystectomy cases. Thus we agree with other surgeons who recommend surgery even for the patient with asymptomatic gallbladder stones because of its likelihood to harbor occult malignancy [32].

Conclusion

Although GBC incidence in our locality is low, yet prognosis is dismal and survival rate does not exceed 50% in early-stage treated cases. Thus, routine histopathological examinations of all cholecystectomy patients is recommended. Simple or extended cholecystectomy in our experience is the treatment of choice for early GBC discovered accidently in laparoscopic cholecystectomy and further surgery may be needed according to multifactorial issues particularly histopathological stage and grade. The study cases are few, yet they are the available. However, further studies are needed to fully establish guidelines for incidentally discovered GBC during laparoscopic cholecystectomy.

Competing interests: The authors declare that no competing interests exist.
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