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RAPID COMMUNICATION

A clinicopathological analysis in unsuspected gallbladder carcinoma: A report of 23 cases

Li-Ning Xu, Sheng-Quan Zou

Li-Ning Xu, Department of Hepatobiliary Surgery of PLA General Hospital, Beijing 100853, China
Sheng-Quan Zou, Department of General Surgery of Tongji Hospital, Tongji Medical College of Huazhong University of Science and Technology, Wuhan 430030, Hubei Province, China
Correspondence to: Dr. Li-Ning Xu, Department of Hepatobiliary Surgery of PLA General Hospital, 28 Fuxing Road, Beijing 100853, China. chaoyue528@sohu.com
Telephone: +86-10-66936602 Fax: +86-10-66936602
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Abstract

AIM: To study the clinicopathological characteristics of unsuspected gallbladder carcinoma (UGC).

METHODS: We retrospectively studied 23 cases of UGC in Tongji Hospital, and compared their clinicopathological characteristics with 33 cases of preoperatively diagnosed gallbladder carcinoma (PDGC).

RESULTS: The proportion of UGC coexisting with cholecystolithiasis was significantly higher than that of PDGC (χ^2 = 13.53, P < 0.01). The infection rate of hepatitis B virus was 21.74% (5/23) in UGC and 30.30% (10/33) in PDGC. Nine (39.13%) of 23 patients with UGC and 8/33 (24.24) PDGC had contact with schistosome pestilent water. The rate of multiple pregnancies was 56.52% (13/23) in the patients with UGC and 42.42% (14/33) in PDGC. The primary location of the UGC was mostly in the neck and body of the gallbladder, and that of the PDGC was often in the body and bottom. The incidence of Nevin stage Ⅰ and Ⅱ UGC was significantly higher than that of PDGC (χ^2 = 4.44, P < 0.05 and χ^2 = 4.96, P < 0.05) while that of Nevin stage Ⅴ UGC was significantly lower than that of PDGC (χ^2 = 7.59, P < 0.01). According to the grading of carcinoma, the incidence of well-differentiated UGC was significantly higher than that of PDGC (χ^2 = 4.16, P < 0.05), and that of poorly-differentiated UGC was significantly lower than that of PDGC (χ^2 = 4.48, P < 0.05).

CONCLUSION: There are different characteristics between UGC and PDGC, such as in primary location, malignant degree and incidence of coexistence with cholecystolithiasis. Cholecystolithiasis, hepatitis B, schistosome and multiple pregnancies were high risk factors for gallbladder carcinoma.

INTRODUCTION

The difficulty in early diagnosis of gallbladder carcinoma results from its poor specificity in clinical symptoms and ambiguous early symptoms, which seriously affects prognosis[1-6]. Some patients were found having gallbladder carcinoma only when they were diagnosed and treated because of other diseases[7-9]. Generally, gallbladder carcinoma is called unsuspected gallbladder carcinoma (UGC) when it was found incidentally during or after cholecystectomy because of gallbladder benign diseases[7,8,10,11]. We consider that UGC still includes gallbladder carcinoma found not only during or after cholecystectomy but also in the course of other diseases[12-17]. UGC found during cholecystectomy because of acute or chronic cholecystitis was reported in 1961[18], but more relative studies and close attention to UGC became available in the 1990s. To date, diagnosis and treatment of UGC still remain difficult[19]. This study aims at defining clinicopathological characteristics of UGC, which may provide some evidence on its diagnosis and treatment.

MATERIALS AND METHODS

Subjects

We retrospectively studied 23 cases of UGC visiting Tongji Hospital from 1990 to 2005, and compared the clinicopathological characteristics with that of 33 cases of PDGC, which included 15 diagnosed cases and 18 suspected cases.

Methods

All specimens were fixed in 4% formaldehyde solution, embedded in paraffin and cut into 4 μm thick sections. And all of them were diagnosed pathologically. Chi-square test and Fisher's exact probability test were used for statistical analysis.

Table 1 Analysis of past history of 23 UGC cases

Indications	UGC	PDGC
Age (yr)	59.57 ± 11.49	56.21 ± 11.62
Sex	M: 5, F: 18	M: 14, F: 19
Signs and symptoms		
Jaundice (*n*)	4	1
Stomachache (*n*)	20	24
Febrile (*n*)	1	1
Dyspepsia (*n*)	4	5
Body weight loss (*n*)	4	6
Abdominal mass (*n*)	0	3
Absence of symptoms (*n*)	1 (preoperative diagnosis is adenoma)	3
Multiple pregnancies (≥ 3 times) (*n*)	13	14
Family malignancy history (*n*)	1, his father suffered with gastric cancer	2, their fathers respectively have lung cancer and hepatoma
Past history		
Gastritis (*n*)	4	3
Gastric ulcer (*n*)	3	2
Hepatitis B (*n*)	5	10
Contact with schistosome pestilent water (*n*)	9	8
Coexisted with cholecystolithiasis (*n*)	17	8[a]
Size of cholecystolithiasis (> 1 cm) (*n*)	7	5
Multiple (*n*)	17	6[b]
Complicated with choledoch carcinoma (*n*)	1	0
Biliary tract diseases found preoperatively		
Polypoid lesion of gallbladder wall (*n*)	3	7
Multiple (*n*)	2	6
Size (> 1 cm) (*n*)	2	3
Gallbladder wall thickening (*n*)	12	9
Gallbladder enlargement (*n*)	5	6
Atrophy of gallbladder (*n*)	2	1
Cholestasis (*n*)	2	0
Congenital capsular dilation of bile duct (*n*)	0	1
Coexist with extra-biliary-tract diseases		
Splenomegaly (*n*)	0	4
Kidney multiple cystis (*n*)	0	2
Hemangiomas of liver (*n*)	0	2
Heparadiposum (*n*)	1	5
Hepatic cirrhosis (*n*)	1	2
Esophageal hiatal hernia (*n*)	0	1
Lateral ventral hernia (*n*)	0	3

[a]$P < 0.01$ ($\chi^2 = 13.53$, *vs* UGC); [b]$P < 0.01$ ($\chi^2 = 17.39$, *vs* UGC).

RESULTS

Analysis of past history

The proportion of UGC coexisting with cholecystolithiasis was significantly higher than that of PDGC ($\chi^2 = 13.53$, $P < 0.01$). The infection rate of hepatitis B virus was 21.74% (5/23) in UGC and 30.30% (10/33) in PDGC. Nine (39.13%) of 23 patients with UGC and 8/33 (24.24) PDGC had contact with schistosome pestilent water. The rate of multiple pregnancies was 56.52% (13/23) in the patients with UGC and 42.42% (14/33) in PDGC. The primary location of the UGC was mostly in the neck and body of the gallbladder, and that of the PDGC was often in the body and bottom. The incidence of Nevin stage Ⅰ and Ⅱ of UGC was significantly higher than that of PDGC ($\chi^2 = 4.44$, $P < 0.05$ and $\chi^2 = 4.96$, $P < 0.05$) while that of Nevin stage Ⅴ UGC was significantly lower than that of PDGC ($\chi^2 = 7.59$, $P < 0.01$). According to the grading of carcinoma, the incidence of well-differentiated UGC was significantly higher than that of PDGC ($\chi^2 = 4.16$, $P < 0.05$), and that of poorly-differentiated UGC was significantly lower than that of PDGC ($\chi^2 = 4.48$, $P < 0.05$) (Table 1).

Condition of diagnosis and treatment

All cases of UGC in this study was found during or after open cholecystectomy, and no case was found during or after laparoscopic cholecystectomy. The ratios of UGC in open cholecystectomy and other cholecystectomies were 0.41% (23/5582) and 0.26% (23/8807), respectively. Preoperative misdiagnoses included cholecystolithiasis, adenoma, and hepatoma in order of frequency (Table 2).

Characteristics of pathology

The proportion of UGC with primary location in neck of gallbladder was significantly higher than that of the PDGC ($P = 0.020$) while the number of UGC with primary location in bottom of gallbladder was significantly lower than that of PDGC ($P = 0.023$). The number of UCG in the bottom and body of gallbladder was significantly lower than that of PDGC ($P = 0.047$). According to Nevin

Table 2 Diagnosis and treatment in 23 UGC cases

Indications	UGC	PDGC
Final diagnosis during operation	60.87% (14/23)	
Final diagnosis after operation	39.13% (9/23)	
Open cholecystectomy	0.41% (23/5582)	
Laparoscopic cholecystectomy	0% (0/3225)	
Imergency operation	13.04% (3/23)	
Main misdiagnosis causes (*n*)		
Hepatoma	2	
Cholecystolithiasis	14	
Adenoma	3	
Cholecystolithiasis coexisted with adenoma	4	
Special examination methods		
USG (*n*)	16	14
CT (*n*)	1	2
MRI (*n*)	0	1
USG + CT (*n*)	3	12
USG + MRI (*n*)	2	3
USG + CT + MRI (*n*)	1	1
Laboratory examinations		
Carcino-embryonic antigen (*n*)	1/2	0/10
Alpha-fetoprotein (*n*)	0/1	2/10
Alkali phosphatase (*n*)	0/0	2/4
γ-GT (*n*)	2/2	2/2
Lactate dehydrogenase (*n*)	0/0	1/1
5-nucleophosphatase (*n*)	0/0	1/1
Operations		
Cholecystectomy (*n*)	17	11
Cholecystectomy + regional lymph clearing (*n*)	2	4
Combined with partial hepatectomy (*n*)	3	10
Combined with partial excision of extrahepatic bile duct (*n*)	1	2
Combined with excision of outer metastasis (*n*)	0	5 (2 cases proved nontumorous metastasis postop)
Exploratory laparotomy (*n*)	0	1
Adjunctive therapy		
Postoperative radiotherapy (*n*)	0	3
Postoperative chemotherapy (*n*)	4	9
Treatment with TCM (*n*)	1	3
TACE with recrudescent tumor (*n*)	0	2

staging, the incidence of stage Ⅰ and Ⅱ was significantly higher in UGC than in PDGC ($\chi^2 = 4.44$, $P < 0.05$ and $\chi^2 = 4.96$, $P < 0.05$) while the incidence of stage Ⅴ was significantly lower in UGC than in PDGC ($\chi^2 = 7.59$, $P < 0.01$). Based on the grading of carcinoma, the incidence of well-differentiated UGC was remarkably higher than that of PDGC ($\chi^2 = 4.16$, $P < 0.05$), and the incidence of poorly-differentiated UGC was significantly lower than that of PDGC ($\chi^2 = 4.48$, $P < 0.05$) (Table 3).

DISCUSSION

The proportion of UGC in gallbladder carcinoma ranged from 22% to 37.5%[20-22], and our result is 41.1% (23/56). The reported incidence of UGC found in open cholecystectomy were 1.7% in Germany[22] and 2.3% in Belgium[23], and it was 0.43% in China[11], and our result is 0.41% which is similar with domestic report.

Our results indicate that cholecystolithiasis play a more important role in the cancerization process of UGC than in PDGC. And hepatitis B, schistosome and multiple pregnancies may affect the cancerization process of gallbladder, which however, needs more evidences and studies in its mechanism. In diagnosis and treatment, our study indicates that there is no significant difference between UGC and PDGC in many aspects, such as age, sex, symptom, signs and complications. All cases of UGC in this study was found during or after open cholecystectomy, and no case was found during or after laparoscopic cholecystectomy. The ratio of UGC found in all cholecystectomies was 0.26% (23/8807). Preoperative misdiagnoses included cholecystolithiasis, adenoma, and hepatoma in order of frequency. These results indicate that more attentions should be paid to cholecystolithiasis, adenoma, and hepatoma in clinical diagnosis.

As for pathological characteristics in our study, the primary location of UGC was mostly in the neck and body of the gallbladder, and that of PDGC was often found in the body and bottom. According to Nevin staging and the grading of gallbladder carcinoma, the proportion of UGC was remarkably lower than PDGC when malignancy degree of carcinoma increased gradually. These results indicate that there are different characteristics between UGC and PDGC in primary location, Nevin staging and tumor grade.

Currently, there are more studies that have began to focus on UGC[24,25], but early diagnosis of gallbladder carcinoma is still difficult[26-30]. In order to improve the diagnosis of gallbladder carcinoma, epidemiological and clinicopathological studies should be conducted. Our

Table 3 Pathological characteristics of 23 UGC cases

Indications	UGC	PDGC
Primary location of gallbladder carcinoma (*n*)	(with record 16 cases)	(with record 21 cases)
Cystic duct	1	1
Neck of gallbladder	8	3[a]
Body of gallbladder	5	6
Bottom of gallbladder	0	6[b]
Boundary between neck and body of gallbladder	2	0
Body and bottom of gallbladder	0	5[c]
Nevin staging		
Ⅰ	6	2[d]
Ⅱ	5	1[e]
Ⅲ	7	8
Ⅳ	2	6
Ⅴ	3	16[f]
Cancerometastasis status (*n*)		
Gallbladder lymph node	1	0
Portal lymph node	0	1
Common bile duct lymph node	1	4
Latero-hepatic artery lymph nod	0	1
Nerve boundle in gallbladder wall	0	2
Extrahepatic bile duct	0	2
Liver	3	11
Diaphragmatic muscle	0	1
Peritoneum	0	1
Omentum	0	1
Pathohistological diagnosis		
Histological type (*n*)		
Adenocarcinoma	20	27
Adenoma canceration	2	2
Squamous carcinoma	1	2
Undifferentiated carcinoma	0	2
Grade (*n*)		
Well differentiated	14	11[g]
Moderately differentiated	3	4
Poorly differentiated	6	18[h]

[a]$P = 0.020$, *vs* UGC; [b]$P = 0.023$, *vs* UGC; [c]$P = 0.047$, *vs* UGC; [d]$P < 0.05$ ($\chi^2 = 4.44$, *vs* UGC); [e]$P < 0.05$ ($\chi^2 = 4.96$, *vs* UGC); [f]$P < 0.01$ ($\chi^2 = 7.59$, *vs* UGC); [g]$P < 0.05$ ($\chi^2 = 4.16$, *vs* UGC); [h]$P < 0.05$ ($\chi^2 = 4.48$, *vs* UGC).

study demonstrates that there are different characteristics between UGC and PDGC in some aspects, which may hopefully provide some beneficial evidence on early diagnosis of gallbladder carcinoma.

COMMENTS

Background

The difficulty in early diagnosis of gallbladder carcinoma results from its poor specificity in clinical symptoms and ambiguous early symptoms, which seriously affect prognosis. Some patients were found having gallbladder carcinoma only when they were diagnosed and treated because of other diseases. To date, diagnosis and treatment in unsuspected gallbladder carcinoma are still difficult. This study aims at clinicopathological characteristics of unsuspected gallbladder carcinoma, which may provide some evidence on its diagnosis and treatment.

Research frontiers

Unsuspected gallbladder carcinoma found during cholecystectomy because of acute or chronic cholecystitis was reported early in 1961, but more relative studies in and close attention to unsuspected gallbladder carcinoma became available after the 1990s. However, its epidemiology and clinicopathology are not well described.

Innovations and breakthroughs

There were different characteristics between unsuspected gallbladder carcinoma and preoperatively diagnosed gallbladder carcinoma, such as in primary location, malignant degree and incidence of coexistence with cholecystolithiasis. Cholecystolithiasis, hepatitis B, schistosome and multiple pregnancies were high risk factors of gallbladder carcinoma.

Applications

In order to improve the diagnosis of gallbladder carcinoma, epidemiology and clinicopathology need be studied. This study indicates that there are different characteristics between unsuspected gallbladder carcinoma and preoperatively diagnosed gallbladder carcinoma in some aspects, which hopefully could provide some beneficial evidence on early diagnosis of gallbladder carcinoma.

Terminology

Unsuspected gallbladder carcinoma (UGC): generally gallbladder carcinoma is called unsuspected gallbladder carcinoma (UGC) when it was found incidentally during or after cholecystectomy. We consider that unsuspected gallbladder carcinoma still includes gallbladder carcinoma found not only during or after cholecystectomy but also in the course of other diseases.

Peer review

The present study is interesting, well designed, and contained novel findings. The conclusions are well based and are of clinical value in some aspects.

REFERENCES

1 **Misra S**, Chaturvedi A, Misra NC, Sharma ID. Carcinoma of the gallbladder. *Lancet Oncol* 2003; **4**: 167-176
2 **Shi JS**, Wang JS, Liu G, Yu YL, Lu Y, Jiao XY, Yang YJ, Li GC, Han Y. Early diagnosis of primary gallbladder carcinoma. *Hepatobiliary Pancreat Dis Int* 2002; **1**: 273-275
3 **Chianakwana GU**, Okafor PI, Anyanwu SN. Carcinoma of the gallbladder at the Nnamdi Azikiwe University Teaching Hospital-a 5-year retrospective study. *Niger J Clin Pract* 2005; **8**: 10-13
4 **de la Cruz J**, Hidalgo LA, Feliu J, Admella C, Muns R, del Bas M, Suñol X. Gallbladder adenocarcinoma: tumoral staging, histological prognostic factors and survival. *Cir Esp* 2005; **77**: 18-21
5 **Zou S**, Zhang L. Relative risk factors analysis of 3,922 cases of gallbladder cancer. *Zhonghua Waike Zazhi* 2000; **38**: 805-808
6 **Misra MC**, Guleria S. Management of cancer gallbladder found as a surprise on a resected gallbladder specimen. *J Surg Oncol* 2006; **93**: 690-698
7 **Samad A**. Gall bladder carcinoma in patients undergoing cholecystectomy for cholelithiasis. *J Pak Med Assoc* 2005; **55**: 497-499
8 **Shimizu T**, Arima Y, Yokomuro S, Yoshida H, Mamada Y, Nomura T, Taniai N, Aimoto T, Nakamura Y, Mizuguchi Y, Kawahigashi Y, Uchida E, Akimaru K, Tajiri T. Incidental gallbladder cancer diagnosed during and after laparoscopic cholecystectomy. *J Nippon Med Sch* 2006; **73**: 136-140
9 **Yeh CN**, Jan YY, Chen MF. Management of unsuspected gallbladder carcinoma discovered during or following laparoscopic cholecystectomy. *Am Surg* 2004; **70**: 256-258
10 **Yamamoto H**, Hayakawa N, Kitagawa Y, Katohno Y, Sasaya T, Takara D, Nagino M, Nimura Y. Unsuspected gallbladder carcinoma after laparoscopic cholecystectomy. *J Hepatobiliary Pancreat Surg* 2005; **12**: 391-398
11 **Tian H**, Chen L, Liu GJ, Liang G, Cao LP, Lin HT, Peng SY. Surgical treatments of preoperative unsuspected gallbladder carcinoma. *Zhonghua Waike Zazhi* 2005; **43**: 836-838
12 **Gertsch P**, Thomas P, Baer H, Lerut J, Zimmermann A, Blumgart LH. Multiple tumors of the biliary tract. *Am J Surg* 1990; **159**: 386-388
13 **Chijiiwa K**. Synchronous carcinoma of the gall-bladder in patients with bile duct carcinoma. *Aust N Z J Surg* 1993; **63**: 690-692
14 **Washburn WK**, Lewis WD, Jenkins RL. Liver transplantation with incidental gallbladder carcinoma in the recipient hepatectomy. *HPB Surg* 1994; **8**: 147-149
15 **Moser JJ**, Baer HU, Glättli A, Schweizer W, Blumgart LH,

Czerniak A. Mirizzi syndrome--a contraindication for laparoscopic surgery. *Helv Chir Acta* 1993; **59**: 577-580
16 **Redaelli CA**, Büchler MW, Schilling MK, Krähenbuhl L, Ruchti C, Blumgart LH, Baer HU. High coincidence of Mirizzi syndrome and gallbladder carcinoma. *Surgery* 1997; **121**: 58-63
17 **Ayhan A**, Guney I, Saygan-Karamursel B, Taskiran C. Ovarian metastasis of primary biliary and gallbladder carcinomas. *Eur J Gynaecol Oncol* 2001; **22**: 377-378
18 **Marcial-Rojas RA**, Medina R. Unsuspected carcinoma of the gallbladder in acute and chronic cholecystitis. *Ann Surg* 1961; **153**: 289-298
19 **Paolucci V**, Neckell M, Götze T. Unsuspected gallbladder carcinoma--the CAE-S/CAMIC registry. *Zentralbl Chir* 2003; **128**: 309-312
20 **Andersson A**, Bergdahl L, Zeuchner E. Carcinoma as an unexpected histologic diagnosis in gallbladder disease (author's transl). *Zentralbl Chir* 1976; **101**: 1314-1317
21 **Kaul V**, Wani NA, Paljor YD. Primary carcinoma of gall bladder-a review of thirty six cases. *Indian J Pathol Microbiol* 1989; **32**: 146-151
22 **Orth K**, Kunz R, Staib L, Beger HG. Gallbladder carcinoma as an incidental finding. *Z Gastroenterol* 1991; **29**: 631-636
23 **Bosmans E**, Onsea J, Verboven H. Gallbladder cancer as unexpected finding at cholecystectomy for benign disease. *Acta Chir Belg* 1990; **90**: 207-212
24 **Cucinotta E**, Lorenzini C, Melita G, Iapichino G, Currò G. Incidental gall bladder carcinoma: does the surgical approach influence the outcome? *ANZ J Surg* 2005; **75**: 795-798
25 **Ciulla A**, Romeo G, Genova G, Tomasello G, Agnello G, Cstronovo G. Gallbladder carcinoma late metastases and incisional hernia at umbilical port site after laparoscopic cholecystectomy. *G Chir* 2006; **27**: 214-216
26 **Goetze T**, Paolucci V. Does laparoscopy worsen the prognosis for incidental gallbladder cancer? *Surg Endosc* 2006; **20**: 286-293
27 **Lam CM**, Yuen AW, Wai AC, Leung RM, Lee AY, Ng KK, Fan ST. Gallbladder cancer presenting with acute cholecystitis: a population-based study. *Surg Endosc* 2005; **19**: 697-701
28 **Oikarinen H**. Diagnostic imaging of carcinomas of the gallbladder and the bile ducts. *Acta Radiol* 2006; **47**: 345-358
29 **Cangemi V**, Fiori E, Picchi C, De Cesare A, Cangemi R, Galati G, Volpino P. Early gallbladder carcinoma: a single-center experience. *Tumori* 2006; **92**: 487-490
30 **Meriggi F**. Gallbladder carcinoma surgical therapy. An overview. *J Gastrointestin Liver Dis* 2006; **15**: 333-335

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