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Original Article

Clinical, pathological and sonographic characteristics of unexpected gallbladder carcinoma

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Abstract: Objectives: To investigate the clinical, pathological, and sonographic characteristics of unexpected gallbladder carcinoma (UGC). Methods: Of 5424 patients who had undergone cholecystectomy from December 2006 to October 2013, 54 patients with primary gallbladder carcinomas confirmed by pathological diagnosis were identified. The patients were divided into two groups: diagnosed before operation (n=34) and UGC groups (n=20), of whom the clinical, pathological, and sonographic characteristics were compared. Results: No significant differences in age, gender, location of lesion, histological type, length of the gallbladder, existence of biliary sludge, and intestinal gas interference between the two groups were found (all $P>0.05$). The clinical symptoms, laboratory abnormalities, tumor markers, coexisting gallbladder stones, lesion size, lesion type, degree of differentiation, and tumor staging showed statistically significant differences between the two groups (all $P<0.05$). On ultrasound, the width of the gallbladder, gallbladder wall thickness, vascularity on color Doppler ultrasound, and bile volume in the gallbladder showed significant differences (all $P<0.05$). Conclusions: UGCs are commonly found at an early stage, often well-differentiated, wall thickened, and are generally accompanied with cholelithiasis. UGCs should be taken into consideration in cases with cholelithiasis or small gallbladder on ultrasound.

Keywords: Unexpected gallbladder carcinoma, diagnosis, ultrasound, clinical characteristics, pathological characteristics

Introduction

Gallbladder carcinomas that have not been identified before the operation but identified during or after the operation are called unexpected gallbladder carcinoma (UGC) [1]. The major causes for the difficulty in detecting UGC lie in the following aspects: difficulty in early diagnosis of gallbladder carcinoma using the current imaging techniques, coexisting cholecystolithiasis or cholecystitis, and difficulty in differential diagnosis between UGC and other benign gallbladder lesions. Previous studies have reported that the incidence of UGC is about 0.309% [2, 3] and UGC accounts for 15-30% of all the gallbladder malignant lesions [3, 4]. Gallbladder cancer always has a dismal prognosis and early diagnosis is the only way to improve the long-term outcome. On the other hand, accurate detection of UGC before operation is essential for choosing the correct surgical method and avoiding secondary re-operation. It was hypothesized that typical gallbladder cancer and UGC might have different clinicopathological or sonographic features. To confirm the hypothesis, the data in a tertiary university hospital were retrospectively analyzed, the aim of which was to find some clues for the diagnosis of UGC and finally improve the prognosis of the patients.

Methods and materials

Patients

The data of 5424 patients who had undergone cholecystectomy between December 2006 and October 2013 in the tertiary university hospital were retrospectively reviewed. Of those, 54 (1%) patients with gallbladder carcinoma, which

was confirmed by postoperative pathological examinations, were identified. Among these 54 patients, 18 were men and 36 were women; a male-to-female ratio was 1:2. The mean age of the patients was 66.0±11.8 years (range: 47 to 88 years). The preoperative diagnoses of 34 patients were suspicious of gallbladder cancers that all were depicted as space-occupying lesions in the gallbladders on imaging studies. Among them, 9 patients had coexisting cholelithiasis and acute inflammation, 14 patients had coexisting cholelithiasis and chronic inflammation, 1 patient had choledocholith, and 1 patient had gallbladder polyps. The other 20 patients were UGCs, who underwent operation due to benign diseases (7 patients with cholelithiasis accompanied with acute inflammation, 12 patients with cholelithiasis accompanied with chronic inflammation and 1 patient with choledocholith).

Ultrasound examination was performed routinely in 35 patients before the operation, while the other 19 patients who underwent emergent operations did not receive preoperative ultrasound examination. Surgical findings and pathological results were used as the reference standard, and then the patients were divided into two groups, namely diagnosed group (i.e. Suspicious of malignancy before operation) and UGC group, respectively. General data, results of laboratory examination, pathological results, and ultrasound images of the patients were retrospectively analyzed.

Equipment and methods

Ultrasound examination: Color Doppler ultrasound devices including GE LOGIQ-E9 (GE Healthcare, Milwaukee, WI, USA), Phillips IU 22 (Philips Medical Systems, Bothell, Wash, USA), Siemens S2000 (Siemens Medical Solutions, Mountain View, CA, USA), and GE Voluson 730 (GE Healthcare, Milwaukee, WI, USA) were used for the ultrasound examinations. Abdominal convex array probe or high-frequency linear array probe was used. The patients routinely underwent fasting for 8 h before the examination. The documented ultrasound images of the patients were retrospectively reviewed, and the size of the gallbladder (the maximum length-diameter and transverse-diameter), thickness of the gallbladder wall, shape, boundary, and vascularity in the lesion (classified as abundant, scarce, and none) were recorded. The biliary sludge, intestinal gas interference, and the amount of the bile were also reviewed from the images. The amount of the bile was classified as no bile, <1/3, and >1/3 according to the volume of bile in the gallbladder.

Laboratory examinations: Laboratory examinations including tumor biomarkers (including carcinoembryonic antigen, CA125, CA153, CA199, and CA724; an increase in one of these biomarkers was considered as abnormal) and blood routine examinations (including white blood cell count and neutrophil count) were reviewed.

Pathological examinations: The locations of the lesions included the neck, body, bottom, and the whole gallbladder; the morphological types of the lesion included thickened-wall type, nodular type, and mass type; histological types of the lesion included adenocarcinoma, adenosquamous carcinoma, severe atypical hyperplasia, and cancer of the glandular epithelium, and others; the degree of differentiation included well differentiated, moderately differentiated, and poorly differentiated.

Staging of the gallbladder carcinoma: According to the tumor-node-metastasis staging criteria (7 edition) issued by the American Joint Committee on Cancer (AJCC) in 2009, the gallbladder carcinomas were classified into four categories (T0-T4) [5] as follows: T0 and T1: tumor invades the lamina propria; T2: tumor invades the connective tissues around the muscular layer of the gallbladder wall but does not invade the serosal layer or liver; T3: tumor invades through the serosal layer and/or directly invades the liver and/or one of the adjacent organ or structure; and T4: tumor invades the main portal vein, hepatic artery, or two or more extrahepatic organs or structures.

Statistical analysis

The SPSS 19.0 software (SPSS Inc., Chicago, Illinois, USA) was used for the statistical analysis. The quantitative data were expressed as mean ± standard deviation. The comparison between the quantitative data was tested using the independent sample *t*-test. The comparison between enumeration data was tested using the Chi-square test or Fisher's exact probability test. $P<0.05$ was considered statistically significant.

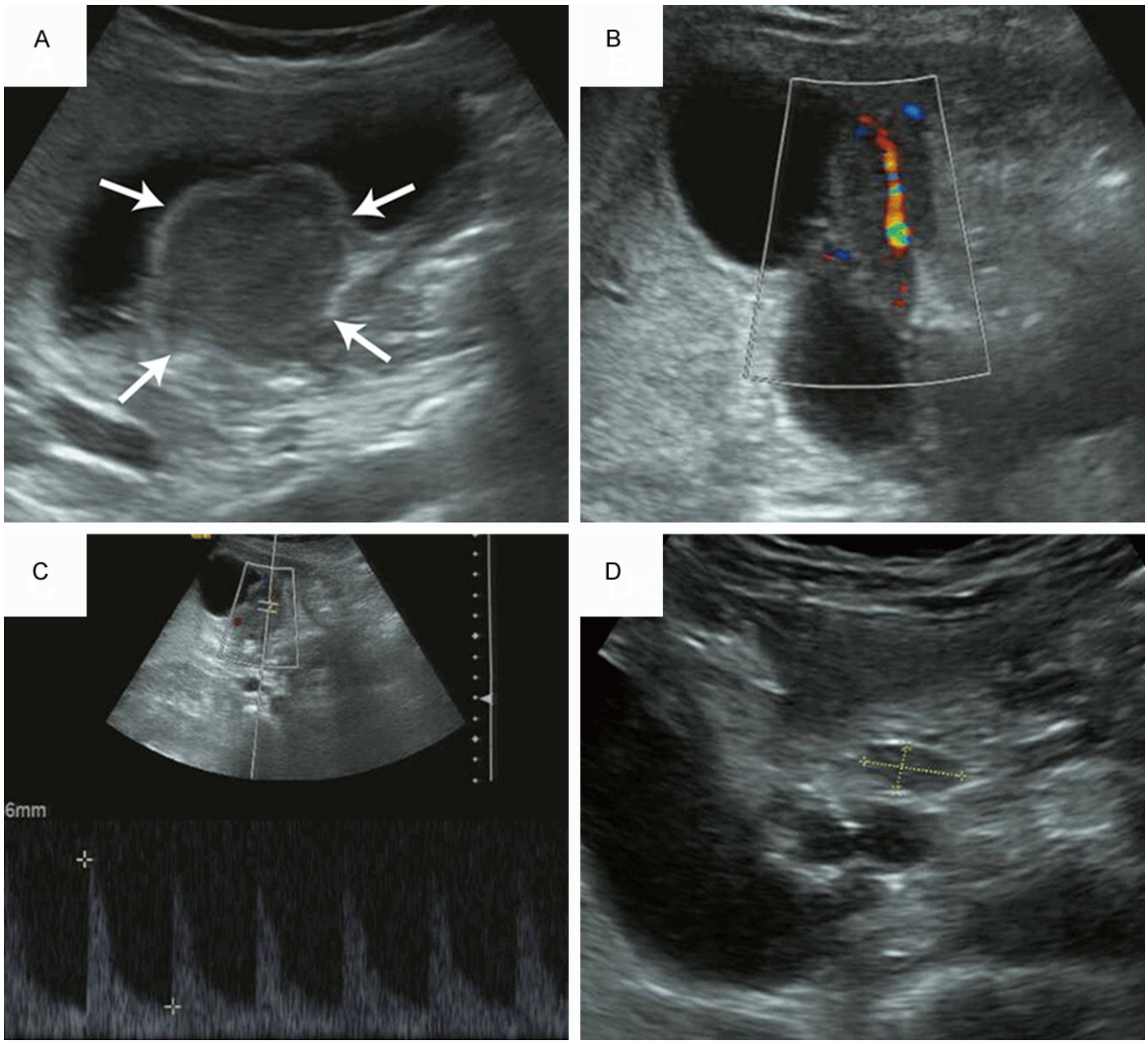

Figure 1. A and B. These two images are from the same patient. A hypoechoic mass at the body of the gallbladder shows intralesional branching blood flow (arrows). Pathological examination suggests moderately to poorly differentiated ulcerative adenosquamous carcinoma that infiltrates all the layers of the gallbladder wall; C. A patient with thickened-wall type of gallbladder carcinoma; focal thickening of the body and bottom of the gallbladder are shown; pathological examination suggests poorly differentiated adenocarcinoma that infiltrated all the layers of the gallbladder wall. D. The mass at the bottom of the gallbladder with inhomogeneous echo inside the lesion and branched blood flow around the lesion; pathological examination suggests poorly differentiated squamous cell carcinoma with a lot of necrosis and infiltration of all the layers of the gallbladder wall as well as liver tissues.

Results

Diagnosis and treatment of the patients

In the diagnosed group, space-occupying lesions were detected using both ultrasound (US) and computed tomography (CT)/magnetic resonance imaging (MRI) in 17 patients, using only US in 5 patients, using only CT/MRI in 3 patients, and using none of US or CT/MRI in 9 patients before surgery (**Figure 1**). All were suspicous of gallbladder malignancy. Cholecystectomy, radical cholecystectomy, and extended radical cholecystectomy were performed in 2, 26, and 3 patients, respectively. Palliative treatment was performed in the remaining three patients.

In the UGC group, 9 patients underwent US and CT/MRI examination, 9 patients underwent CT/MRI examination and 2 patients underwent US, all of them were diagnosed mistakenly. Nine patients were not diagnosed as gallbladder carcinomas, but diagnosed as cholecystolithiasis,

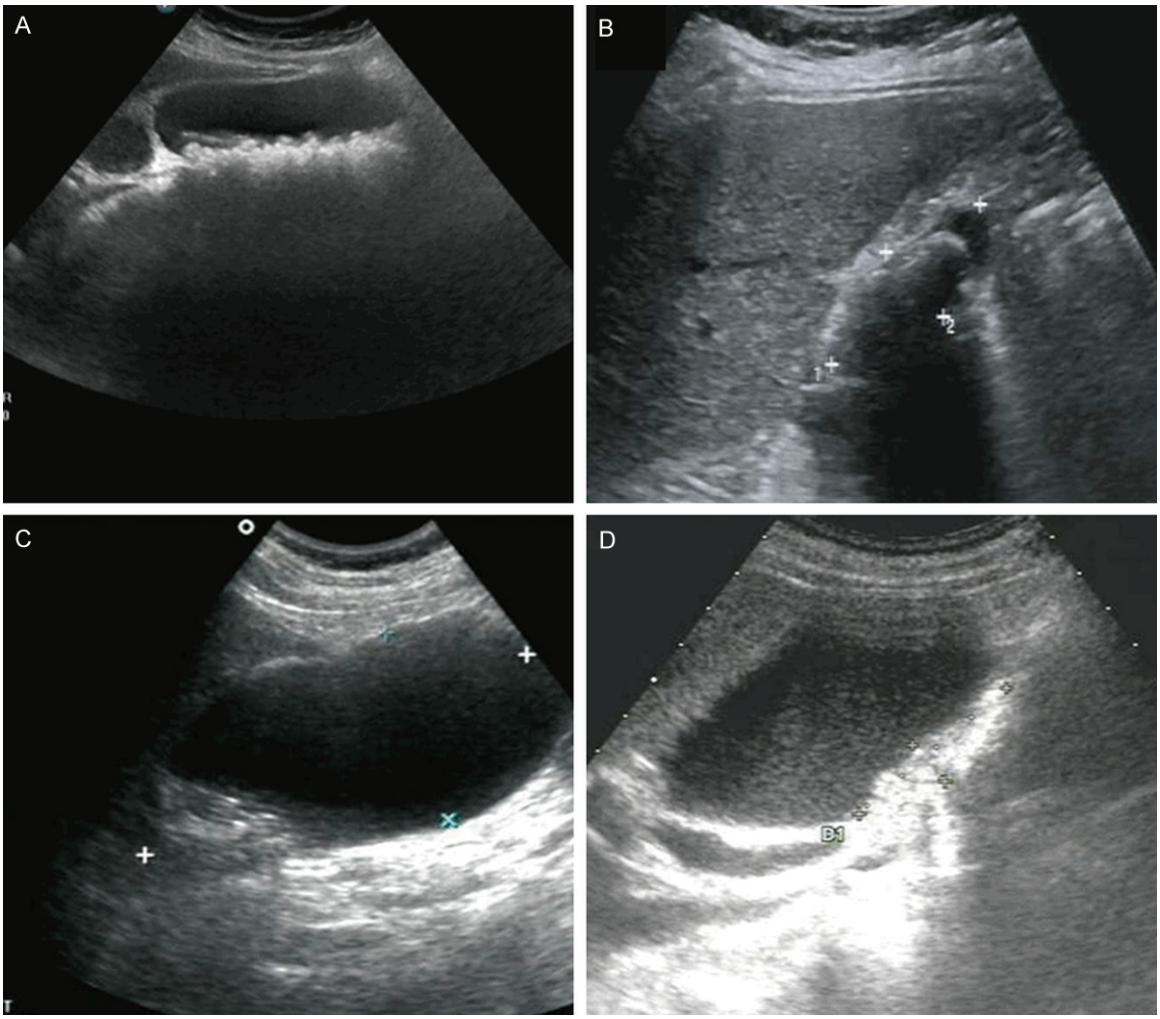

Figure 2. A. Preoperative ultrasound examination shows gallbladder enlargement and multiple cholecystolithiasis; postoperative pathological examination shows moderately differentiated adenocarcinoma at the bottom of the gallbladder that infiltrated to the muscular layer of gallbladder wall. B. The patient has no symptoms; however, ultrasound examination during routine physical examination shows cholecystolithiasis and atrophic gallbladder; pathological examination shows that the thickness of the gallbladder wall was 3-5 mm, moderate to poorly differentiated adenocarcinoma, and infiltration of all the layers of the gallbladder wall. C. The patient is diagnosed with incarcerated calculi at the gallbladder neck and acute cholecystitis; pathological examination shows poorly differentiated adenocarcinoma with liver partially. D. The patient is diagnosed as cholecystolithiasis with enlarged gallbladder; pathological examination shows moderately to poorly differentiated adenocarcinoma at the gallbladder body.

cholecystitis, or choledocholith using ultrasound, CT, or MRI examination. Eight patients underwent cholecystectomy (including cholecystectomy and stone extraction from the common bile duct in one patient) and 12 patients underwent laparoscopic cholecystectomy (including nine patients who switched to laparotomic radical cholecystectomy immediately after the results of intraoperative frozen pathological examination suggested gallbladder carcinoma and one patient who underwent pancreaticoduodenectomy) (**Figure 2**).

The clinical and pathological characteristics of the gallbladder carcinomas were shown in **Table 1**. The age, sex, locations of the lesions, and histological types of the lesions were not significantly different between the diagnosed group and the UGC group. In contrast, presence or absence of clinical symptoms, increase in white blood cell count, abnormal tumor biomarkers, accompanying cholecystolithiasis, size of the lesion, the morphological type of lesion, degree of differentiation, and AJCC staging of the tumor were significantly different

Table 1. Clinical and pathological characteristics of the gallbladder carcinomas

Characteristics	Diagnosed group (n=34)	UGC group (n=20)	*P* value
Patient			
Gender (Male/Female)	9/25	9/11	0.163
Age (yrs)	65.9±12.9	69.1±10.8	0.364
Clinical symptomatic			
Abdominal discomfort	13	14	0.024*
Fever	1	2	
Jaundice	3	2	
Asymptomatic	17	2	
White blood cells (Higher /normal)	16/14[a]	6/10[a]	0.031*
Tumor markers (Abnormal/normal)	23/11	7/13	0.002*
Coexisting gallbladder stones (Present/Absent)	23/11	19/1	0.022*
Infiltrating the gallbladder wall (Local/Diffuse)	24/10	19/1	0.039*
Gallbladder size			
Length (mm)	33.6±24.5	24.4±8.6	0.214
Width (mm)	24.7±15.9	12.9±5.9	0.001*
Lesion location			
Neck	9	10	0.113
Body	5	4	
Bottom	10	5	
All	10	1	
Morphological type			
Thickened-wall type	8	13	0.001*
Nodular type	8	6	
Mass type	18	1	
Histological type			
Adenocarcinoma	28	14	0.066
Adenosquamous carcinoma	3	1	
Severe atypical hyperplasia and cancerization of the glandular epithelium	1	5	
Others	2[b]	0	
Degree of differentiation			
Well differentiated	5	9	0.032*
Moderately differentiated	16	8	
Poorly differentiated	13	3	
Stage (AJCC)			
T1	4	9	0.042*
T2	15	4	
T3	12	6	
T4	3	1	

Note-*: Indicates statistically significant difference; a: Indicates 4 cases without blood routine examination; b: Indicates 1 case of carcinosarcoma and 1 case of squamous cell carcinomas.

between the two groups (all $P<0.05$). However, as the clinical symptoms including right upper abdominal pain, fever, and the increase in the white blood cell count were very similar to the presentations in acute or chronic cholecystitis and cholecystolithiasis, thus the symptoms were non-specific.

In contrast to the diagnosed group, the lesion sizes in the UGC group were relatively small, the degree of differentiation was high, and most of the lesions were thickened-wall type; in addition, the whole gallbladder wall was invaded in only one patient, while the invasion was relatively superficial and focal. Most of the lesions

Table 2. Sonographic characteristics of the gallbladder carcinomas

Characteristics	Diagnosed group (n=24)	UGC group (n=11)	*P* value
Gallbladder size			
Length (mm)	84.7±22.7	79.1±27.2	0.423
Width (mm)	41.6±12.7	32.3±10.8	0.009*
Gallbladder wall thickness (mm)	8.0±4.6	5.5±1.6	0.016*
Vascularity			
None	9	10	0.012*
Scarce	8	1	
Abundant	7	0	
Amount of bile in gallbladder			
None	2	6	0.012*
<1/3	9	2	
>1/3	13	3	
The biliary sludge			
Present/Absent	5/19	4/7	0.416
Intestinal gas interference	20/4	10/1	1.000

Note-*: Indicates statistically significant difference.

in the UGC group were at stage T1 or T2, including five patients with severe atypical hyperplasia and cancer of the gallbladder glandular epithelium with the infiltration of only mucous and muscular layers.

Sonographic characteristics

Overall, 24 patients in the diagnosed group and 11 patients in the UGC group underwent preoperative ultrasound examinations (**Table 2**, **Figures 1**, **2**).

As shown in **Table 2**, the width of the gallbladder, thickness of the gallbladder wall, vascularity, and the amount of bile were significantly different between the two groups (all $P<0.05$). With regard to the features of the ultrasound images in the UGC group, the width of the gallbladder seemed to be small, the thickening of the gallbladder wall was not obvious, most lesions were without vascularity (n=10), the amount of bile in the gallbladder was mainly poor (n=2) or none (n=6), which accounted for 72.7% of all the lesions in this group. In addition, one patient had liver abscess and another had acute pancreatitis.

Discussion

Gallbladder cancer has geographic and ethnic variation throughout the world and is a highly fatal malignant tumor. The poor prognosis of this disease is due to the anatomic position of the gallbladder and the nonspecific symptoms and signs [6, 7]. These characteristics of gallbladder cancer result in advanced primary tumors and lymph node metastasis by the time of diagnosis [8], at which time the best opportunity for operation would have been lost. Although surgical technologies have improved greatly during the recent years, the 5-year survival rate in patients with gallbladder carcinoma has not improved significantly. One important reason for this phenomenon is that only 24% of the patients with early-stage gallbladder carcinoma have been clinically treated [9]. Therefore, reducing the rate of misdiagnosis or missed diagnosis and improving the rate of early diagnosis are the issues that need to be solved urgently. In this study, the clinical, pathological, and ultrasound features of 34 patients with preoperatively diagnosed gallbladder carcinomas and 20 patients with UGCs were compared; the reasons for misdiagnosis or missed diagnosis of UGC were analyzed.

Most of the UGCs were at early stage in this study. As shown in **Table 1**, the whole gallbladder wall was infiltrated in 10 patients of the diagnosed group, but in only 1 patient of the UGC group; in addition, most (65%) of the patients in the UGC group were in stage T1 or T2 carcinoma, including 9 patients in stage T1, 4 patients in stage T2 carcinoma, 5 patients had severe atypical hyperplasia and cancer of the glandular epithelium. In the UGC group, only mucous and muscular layers were infiltrated, while the serosal layer and adjacent liver were not invaded. Kang et al [10] suggested that simple cholecystectomy is sufficient for stage I or II gallbladder carcinoma. In addition, a study showed that this operation could result in a 5-year survival rate up to 100% [11].

Most of the UGCs are accompanied with cholecystolithiasis. A large number of clinical studies demonstrated that cholecystolithiasis could induce gallbladder carcinoma. A previous study

showed that 69% to 100% of the patients with gallbladder carcinoma also had cholecystolithiasis; the incidence of gallbladder carcinoma was about 4.5% to 14% in patients with cholecystolithiasis [12]. In the present study, 77.8% of the patients with gallbladder carcinomas had cholecystolithiasis, which was in accordance with previous report. In addition, 67.7% of the patients in the diagnosed group had cholecystolithiasis (23/34), while 95% of the patients in the UGC group had cholecystolithiasis (19/20). In the UGC group, two patients with the calculus at the gallbladder neck, three patients accompanied with choledocholith, four patients with stuffed cholelithiasis, and nine patients with multiple cholecystolithiasis. The reasons for missed diagnosis were partly due to the acoustic shadowing caused by the gallbladder stones, which masked the display of UGC; in addition, the investigator are always satisfied with the diagnosis of cholecystolithiasis or cholecystitis only; they ignore the possibility of gallbladder carcinoma. Therefore, the investigator should ask the patients to change their body positions to scan from different directions to examine the gallbladder wall that might be masked by the shadows of the stones. The continuity, integrity of the gallbladder wall, as well as suspicious thickened gallbladder wall, should be carefully evaluated. According to previous studies [13, 14], the high risk factors of cancer from cholecystolithiasis include: (1) age ≥60 years, especially in women; (2) duration of cholecystolithiasis >10 years; (3) diameter of cholecystolithiasis >2.0 cm, or stuffed gallstone; (4) incarcerated stones at the gallbladder neck; (5) focal thickening of the gallbladder wall; (6) pain due to cholecystolithiasis changing from intermittent to continuous; (7) accompanied with polypoid lesion of the gallbladder; (8) nonfunctional gallbladder or porcelain gallbladder; and (9) atrophic cholecystitis or calcification of the gallbladder wall. In patients with these high-risk factors, alert should be increased to rule out the possibility of malignancy.

In the present study, thickened-wall type was found in 65% (13/20) of UGCs, while only in 23.5% (8/34) of diagnosed group. The thickness of the gallbladder wall, however, was more obvious (8.0 mm) in the diagnosed group than in the UGC group (5.5 mm). These findings suggest that UGCs always have mildly thickened gallbladder wall and it is difficult to distinguish them from the inflammatory thickening of the gallbladder walls using conventional ultrasound; therefore, high-frequency ultrasound, contrast-enhanced ultrasound, or even endoscopic ultrasound should be performed in suspicious cases [15-18]. With regard to the location of the lesions, a half of the UGCs were found in the gallbladder neck (50%, 10/20), although there was no significant difference between the two groups. Gallbladder neck is in an anatomically "busy" area due to the presence of adjoining bile duct, portal vein, liver, duodenum, and colon [19, 20]. Therefore, the neck of the gallbladder should be carefully examined during ultrasound examination and the reasons for enlargement of the gallbladder should be searched if present. On the other hand, the amount of bile in the gallbladder was significantly different between the diagnosed group and UGC group. The small amount of bile for UGC increases the difficulty to detect the UGC since bile in gallbladder is always served as a good acoustic window for ultrasound examinations. Therefore, attention should be paid in cases of gallbladder with small amount of bile.

The study has some limitations: This was a retrospective study thus a selection bias might be present. The imaging data of several patients were not available due to emergent operation, therefore the features on conventional ultrasound examinations were not evaluated, and also the images obtained from ultrasound examinations were not compared with CT and MRI images.

In summary, UGCs are commonly found at an early stage, often well-differentiated, wall thickened, and are generally accompanied with cholelithiasis. UGCs should be taken into consideration in cases with cholelithiasis or small gallbladder on ultrasound.

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Disclosure of conflict of interest

None.

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References

[1] Varshney S, Butturini G, Gupta R. Incidental carcinoma of the gallbladder. Eur J Surg Oncol 2002; 28: 4-10.

[2] Contini S, Dalla VR, Zinicola R. Unexpected gallbladder cancer after laparoscopic cholecystectomy: an emerging problem? Reflections on four cases. Surg Endosc 1999; 13: 264-267.

[3] Frauenschuh D, Greim R, Kraas E. How to proceed in patients with carcinoma detected after laparoscopic cholecystectomy. Langenbecks Arch Surg 2000; 385: 495-500.

[4] Steinert R, Nestler G, Sagynaliev E, Muller J, Lippert H, Reymond MA. Laparoscopic cholecystectomy and gallbladder cancer. J Surg Oncol 2006; 93: 682-689.

[5] Choi BG, Kim CY, Cho SH, Kim HJ, Koh YS, Kim JC, Cho CK, Kim HJ, Hur YH. Impact of lymph node ratio as a valuable prognostic factor in gallbladder carcinoma, focusing on stage IIIB gallbladder carcinoma. J Korean Surg Soc 2013; 84: 168-177.

[6] Dutta U. Gallbladder cancer: can newer insights improve the outcome. J Gastroenterol Hepatol 2012; 27: 642-653.

[7] Jayaraman S, Jarnagin WR. Management of gallbladder cancer. Gastroenterol Clin North Am 2010; 39: 331-342.

[8] Yang XW, Yang J, Li L, Man XB, Zhang BH, Shen F, Wu MC. Analysis of the relationships between clinicopathologic factors and survival in gallbladder cancer following surgical resection with curative intent. PLoS One 2012; 7: e51513.

[9] Goetze TO, Paolucci V. The prognostic impact of positive lymph nodes in stages T1 to T3 incidental gallbladder carcinoma: results of the German Registry. Surg Endosc 2012; 26: 1382-1389.

[10] Kang CM, Choi GH, Park SH, Kim KS, Choi JS, Lee WJ, Kim BR. Laparoscopic cholecystectomy only could be an appropriate treatment for selected clinical R0 gallbladder carcinoma. Surg Endosc 2007; 21: 1582-1587.

[11] Cui HX, Ma XD, Han XL, Zhang XH. Surgical strategies for unexpected gallbladder carcinoma. Eur Rev Med Pharmacol Sci 2014; 18: 3045-3047.

[12] Alexander S, Lemmens VE, Houterman S, Nollen L, Roumen R, Slooter GD. Gallbladder cancer, a vanishing disease. Cancer Causes Control 2012; 23: 1705-1709.

[13] Vijayakumar A, Vijayakumar A, Patil V, Mallikarjuna MN, Shivaswamy BS. Early diagnosis of gallbladder carcinoma: an algorithm approach. ISRN Radiol 2013; 2013: 239424.

[14] Shrikhande SV, Barreto SG, Singh S, Udwadia TE, Agarwal AK. Cholelithiasis in gallbladder cancer: coincidence, cofactor, or cause. Eur J Surg Oncol 2010; 36: 514-519.

[15] Liu LN, Xu HX, Lu MD, Xie XY, Wang WP, Hu B, Yan K, Ding H, Tang SS, Qian LX, Luo BM, Wen YL. Contrast-enhanced ultrasound in the diagnosis of gallbladder diseases: a multi-center experience. PLoS One 2012; 7: e48371.

[16] Xie XH, Xu HX, Xie XY, Lu MD, Kuang M, Xu ZF, Liu GJ, Wang Z, Liang JY, Chen LD, Lin MX. Differential diagnosis between benign and malignant gallbladder diseases with real-time contrast-enhanced ultrasound. Eur Radiol 2010; 20: 239-248.

[17] Zheng SG, Xu HX, Liu LN, Lu MD, Xie XY, Wang WP, Hu B, Yan K, Ding H, Tang SS, Qian LX, Luo BM. Contrast-enhanced ultrasound versus conventional ultrasound in the diagnosis of polypoid lesion of gallbladder: a multi-center study of dynamic microvascularization. Clin Hemorheol Microcirc 2013; 55: 359-374.

[18] Sparchez Z, Radu P. Role of CEUS in the diagnosis of gallbladder disease. Med Ultrason 2012; 14: 326-330.

[19] Pilgrim CH, Usatoff V, Evans P. Consideration of anatomical structures relevant to the surgical strategy for managing gallbladder carcinoma. Eur J Surg Oncol 2009; 35: 1131-1136.

[20] Kondo S, Hirano S, Tanaka E, Tsuchikawa T, Kato K, Matsumoto J, Nasu Y, Shichinohe T. Two types of extended liver resection for advanced gallbladder cancer: how to do it. Dig Surg 2011; 28: 148-153.