Clinical Significances of Chronic Cholecystitis according to Gallbladder Contraction

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Background/Aims: Chronic cholecystitis and contraction of gallbladder (GB) have been regarded as precancerous lesions. The aim of study is to clarify whether chronic cholecystitis and GB contraction have clinical significance.

Methods: This study included 409 patients underwent cholecystectomy for chronic cholecystitis between January 2006 and June 2011 at a single center. Data regarding radiologic findings and blood tests were collected retrospectively.

Results: About 384 patients (94%) had GB stones. Among 409 patients, 104 (25.4%) patients had contracted GB and 305 (74.6%) patients did not. Biliary pain was more common in the contracted GB group (42.3% vs. 31.1%). The contracted GB group had a higher proportion of diffuse wall thickening type and a higher conversion rate to open cholecystectomy. Only seven patients (1.7%) were finally diagnosed with GB cancers. All patients were over 60 years of age and complained of biliary pain; however, only one patient had contraction of GB.

Conclusions: Biliary pain, diffuse wall thickening, and conversion to open cholecystectomy were more frequent in the contracted GB group. Although incidental GB cancers were rarely diagnosed, all were older and had biliary pain. These will be used as significant evidences when making a treatment plan in chronic cholecystitis and contracted GB.


Keywords: Gallbladder, Cholecystitis, Gallbladder cancer
INTRODUCTION

Chronic cholecystitis, a common form of gallbladder (GB) inflammation that is usually associated with gallstones, is one of the most prevalent diseases requiring surgical intervention. Chronic GB inflammation gives rise to effects such as thickening of the GB wall and GB contraction. Although GB wall thickening can be due to various conditions, chronic GB inflammation is known to lead to thickening of the GB wall. When a GB is chronically contracted, it is regarded to be a result of long-standing chronic cholecystitis. Chronic cholecystitis is typically diagnosed by ultrasonography and computed tomography (CT) based on a distended or contracted GB and the absence of pericholecystic inflammatory stranding or fluid. Imaging studies usually reveal diffuse thickening of the GB wall; however, thickening is sometimes localized to a focal portion of the wall. Chronic cholecystitis that results from chronic inflammation might be a major factor triggering early metaplastic changes in the GB epithelium, because repeated inflammation is one of the causes of carcinogenesis. Furthermore, in contraction of GB resulting from long-standing chronic cholecystitis, cancer-related substances such as iNOS and COX-2 have been found to express strongly and to take part in the development of cellular atypia. As a result, recurrent inflammation of the GB has been regarded as the first step toward carcinogenesis. Therefore, it is necessary to understand the clinical characteristics of chronic cholecystitis with or without GB contraction and the relationship between chronic cholecystitis and GB cancer, although it is difficult to detect premalignant changes. As such, the present study was carried out to clarify whether chronic cholecystitis and contraction of GB, in which thickening of the wall is caused by recurrent inflammation, had clinical significance. In addition, the relationship between chronic cholecystitis with or without contracted GB and GB carcinomas was investigated using the histologic reviews after cholecystectomy.

METHODS

1. Patients

Between January 2006 and June 2011, 7,742 patients suspected of chronic cholecystitis with GB wall thickening were searched retrospectively in the radiologic database of a single center (Asan Medical Center, Seoul, Korea). In order to select only cases of chronic cholecystitis with GB wall thickening, patients with other causes of wall thickening and patients suspected of having other GB diseases were excluded. A total of 7,042 patients were excluded for the following reasons: acute cholecystitis, GB adenomyomatosis, GB polyps, GB cancer, other diseases of the pancreatobiliary system, other malignant diseases, severe systemic diseases, and previous procedures of the pancreatobiliary tract. Of the remaining 700 patients diagnosed with chronic cholecystitis, 409 patients had undergone cholecystectomy. Thus, the 409 patients who had undergone cholecystectomy for chronic cholecystitis were included for analysis (Fig. 1). This retrospective study was approved by the institutional review board of our institution.

2. Definitions

Biliary pain has been defined as intense, dull, pressure-like discomfort in the right upper abdomen, mid-abdomen, or chest that may radiate to the back and right shoulder blade, usually after ingesting a fatty meal. Incidental GB
cancer was defined as a cancer first diagnosed by pathological examination of the GB after cholecystectomy. Chronic cholecystitis is defined by radiologic studies that show GB contraction or distension, thickening of the GB wall, and absence of hepatic hyperemia, pericholecystic inflammatory stranding or fluid collection. GB wall thickening has been defined as a transverse wall ≥3 mm based on ultrasonography and abdominal CT. Type of GB wall thickening was divided into focal or diffuse thickening. Contraction of GB was defined as the totally collapsed lumen of the GB with wall thickening on radiologic findings (Fig. 2).

3. Methods

GB wall thickness was measured at the most thickened portion of the GB. Of the patients in the database who were examined using abdominal ultrasonography and CT, patients with GB wall thickening were enrolled. Detailed medical histories, including history of biliary pain, GB stones, jaundice, and other associated diseases were compiled using patient interviews. Physical measurements and blood test and urinalysis results were also collected. In order to evaluate the clinical significance of contraction of GB in chronic cholecystitis, the patients who had undergone cholecystectomy were divided into two groups according to contraction of GB. The prevalence of incidental GB cancers was also assessed in the patients who underwent cholecystectomy for chronic cholecystitis. Patients who received a final diagnosis of GB cancer were evaluated.

4. Statistical analysis

The data were analyzed using SPSS 18.0 (SPSS Inc., Chicago, IL, USA), and the means ± standard deviation and frequencies (percentage) were determined. The means of the continuous variables were compared using Student’s t test,
and differences between the categorical variables were analyzed using the $\chi^2$ or Fisher’s exact test. Statistical significance was defined as $p<0.05$ (two-tailed).

**RESULTS**

1. Clinical characteristics of chronic cholecystitis patients

Of the 409 patients who underwent cholecystectomy for chronic cholecystitis, the mean age was $48.1 \pm 13.0$ years, and 237 (57.9%) patients were female (Table 1). One hundred thirty-nine (34.0%) patients had biliary pain and 384 (93.9%) patients had GB stones. Among the 25 patients who did not have GB stones, six (25%) patients had biliary pain nonetheless. The results of blood tests—Liver function test (LFT), C-reactive protein (CRP), carbohydrate antigen 19-9 (CA 19-9), and carcinoembryonic antigen (CEA)—were within normal ranges. The focal type of wall thickening was seen in 240 patients (58.7%) and the diffuse type was noted in 169 patients (41.3%). Among the 409 patients, 397 (97.1%) underwent laparoscopic cholecystectomy and only 12 (2.9%) underwent open cholecystectomy. Although laparoscopic cholecystectomy was initially attempted in those 12 patients, they were converted to open cholecystectomy due to operative difficulties. Of the 409 patients diagnosed with chronic cholecystitis on preoperative radiologic studies, 385 (94.1%) were confirmed with chronic cholecystitis by histologic examination. However, four patients were diagnosed with GB adenomyomatosis, three with GB polyps, one with xanthogranulomatous cholecystitis, and nine with cholesterosis of the GB wall. In addition, seven patients (1.7%) received a final diagnosis of GB cancer.

**Table 1.** Clinical characteristics of patients who had chronic cholecystitis with or without contraction of GB

<table>
<thead>
<tr>
<th></th>
<th>Total patients of chronic cholecystitis</th>
<th>Patients with contracted GB</th>
<th>Patients without contracted GB</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (n)</td>
<td>409</td>
<td>104 (25.4)</td>
<td>305 (74.6)</td>
<td>0.086</td>
</tr>
<tr>
<td>Age (y)</td>
<td>48.1±13.0</td>
<td>46.2±12.2</td>
<td>48.7±13.2</td>
<td>0.086</td>
</tr>
<tr>
<td>Sex (M/F)*</td>
<td>172/237</td>
<td>40/64</td>
<td>132/173</td>
<td>0.390</td>
</tr>
<tr>
<td>Biliary pain (n)*</td>
<td>139 (34.0)</td>
<td>44 (42.3)</td>
<td>95 (31.1)</td>
<td>0.017</td>
</tr>
<tr>
<td>GB stones (n)*</td>
<td>384 (93.9)</td>
<td>95 (91.3)</td>
<td>289 (94.8)</td>
<td>0.210</td>
</tr>
<tr>
<td>Wall thickening (focal/diffuse)*</td>
<td>240/169</td>
<td>44/60</td>
<td>196/109</td>
<td>0.001</td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>24.8±16.3</td>
<td>23.5±19.0</td>
<td>26.2±11.8</td>
<td>0.368</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>23.8±27.9</td>
<td>22.9±31.2</td>
<td>24.9±22.3</td>
<td>0.330</td>
</tr>
<tr>
<td>ALP (IU/L)</td>
<td>65.5±25.6</td>
<td>63.3±23.0</td>
<td>67.3±28.9</td>
<td>0.139</td>
</tr>
<tr>
<td>r-GTP (IU/L)</td>
<td>32.9±33.2</td>
<td>34.1±35.8</td>
<td>31.8±30.5</td>
<td>0.447</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>0.9±0.3</td>
<td>0.9±0.3</td>
<td>0.9±0.4</td>
<td>0.910</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>0.76±3.19</td>
<td>0.52±1.27</td>
<td>0.84±3.61</td>
<td>0.483</td>
</tr>
<tr>
<td>CA 19-9 (U/mL)</td>
<td>10.3±14.3</td>
<td>10.2±15.8</td>
<td>10.4±13.0</td>
<td>0.912</td>
</tr>
<tr>
<td>CEA (ng/mL)</td>
<td>1.7±1.7</td>
<td>1.9±2.4</td>
<td>1.5±1.1</td>
<td>0.099</td>
</tr>
<tr>
<td>Operation (LC/Open)</td>
<td>397/12</td>
<td>97/7</td>
<td>300/5</td>
<td>0.014</td>
</tr>
<tr>
<td>GB cancer (n)</td>
<td>7</td>
<td>1</td>
<td>6</td>
<td>0.684</td>
</tr>
<tr>
<td>Histology (chronic cholecystitis/other GB diseases)</td>
<td>385/24</td>
<td>95/9</td>
<td>290/15</td>
<td>0.294</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD or n (%).
GB, gallbladder; M, male; F, female; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; r-GTP, gamma-glutamyl transferase; CRP, C-reactive protein; CA, carbohydrate antigen; CEA, carcinoembryonic antigen; LC, laparoscopic cholecystectomy; Open, open cholecystectomy.

*Sex, symptom, GB stones, wall thickening and contracted GB were analyzed by $\chi^2$ test.
2. Differences in clinical characteristics according to contraction of GB in chronic cholecystitis

The 409 patients who underwent cholecystectomy were divided into two groups according to contraction of GB on the radiologic studies (Table 1): 104 (25.4%) patients had contraction of GB and 305 (74.6%) patients did not. Biliary pain was more common among patients with a contracted GB than among those without a contracted wall (42.3% vs. 31.1%, respectively; \( p=0.017 \)). The proportion of the diffuse type of wall thickening was higher in the contracted GB group than in the non-contracted GB group (57.7% vs. 35.7%, respectively; \( p=0.001 \)). The conversion rate to open cholecystectomy was higher in the contracted GB group than in the non-contracted GB group (6.7% vs. 1.6%, respectively; \( p=0.014 \)). However, the final histologic diagnoses were similar in both groups. The diagnoses in the contracted GB group were 95 patients (94.1%) confirmed with chronic cholecystitis and one patient was GB cancer. In the non-contracted GB group, the final diagnoses were 290 patients with chronic cholecystitis (95.1%) and six with GB cancer. There were no differences in age, sex, or prevalence of GB stones between the groups. Moreover, LFT, CRP, CA 19-9 and CEA did not differ between the groups. According to contraction of GB, the 385 patients, who were finally diagnosed with chronic cholecystitis in histologic examination, were also divided into two groups and analyzed in same method. The analysis of 385 patients showed same conclusions as that of 409 subjects.

3. Clinical characteristics of the GB cancer patients

Seven patients received a final diagnosis of GB cancer among the 409 patients who underwent cholecystectomy for chronic cholecystitis. The patients had no underlying benign GB diseases, such as polyp, adenomyomatosis, or cholelithiasis, before the cholecystectomy. Although all seven patients underwent surgery, no definitive evidence of GB cancer was noted on any examination. However, all cancer patients complained of biliary pain. These patients were older than 60 years of age and included four males and three females. Five of these patients had GB stones, and only one patient had contracted GB on the radiologic findings. Three patients had the diffuse type of wall thickening and four patients had the focal type. There were no differences in wall thickening patterns between the chronic cholecystitis and GB cancer cases. Tumor markers such as CA 19-9 and CEA and other blood tests were within normal ranges. Six patients underwent laparoscopic cholecystectomy; only one patient was converted to open cholecystectomy, due to intra-abdominal adhesion from a previous abdominal surgery. According to the TNM staging system, two patients were diagnosed as stage I and five patients were diagnosed as stage II (Table 2).
DISCUSSION

Chronic cholecystitis almost always occurs in the setting of the cholelithiasis, and it is accompanied by GB wall thickening in many cases. Increased thickness of the GB wall is also a sign of significant inflammatory change. Contraction of GB is known to result from long-standing chronic cholecystitis. Moreover, chronic inflammation of the GB leads not only to radiologic anatomic changes, but also to various histologic changes of the GB wall, including fibrosis, hyperplasia, dysplasia, and metaplasia. Several reports have shown that a lot of GB cancer patients have a history suggestive of chronic cholecystitis. Although chronic inflammation of the GB and contraction of GB have been regarded as precancerous lesions in several studies, there has been no determination of the clinical significance of chronic cholecystitis with or without contraction of GB. In addition, few studies have examined the relationship between chronic cholecystitis with or without GB contraction and incidental GB cancer. Therefore, we identified the clinical characteristics of chronic cholecystitis, contraction of GB, and incidental GB cancers.

According to the current study, about 95% of the chronic cholecystitis patients had GB stones. This result confirmed that chronic cholecystitis occurs most often in the setting of cholelithiasis. In patients with chronic cholecystitis, biliary pain occurs more frequently than those without chronic cholecystitis, although blood tests such as LFT and CRP, as well as tumor marker, were within normal ranges. One-third of the patients in chronic cholecystitis had typical biliary pain, although biliary pain was generally present in 20% of the patients with GB stones. A quarter of patients who had no GB stones also complained of biliary pain. It suggests that the pain was caused by chronic inflammation of the GB in addition to the mechanical obstruction of GB stones. Furthermore, these results indicate that chronic cholecystitis does not induce the systemic problem, but generally leads to regional changes in the GB wall.

We also identified the clinical significance of contracted GB in patients with chronic cholecystitis. Biliary pain was more common among the patients with contraction of GB than in those without it. From a mechanical point of view, the presence of GB stones caused inflammatory changes in the GB wall, such as fibrosis and muscular atrophy, suggesting that the mechanical irritation of GB stones might lead to local inflammation of the GB wall rather than diffuse wall damage. However, the proportion of the diffuse type of wall thickening was higher in the contracted GB group, although the focal type was observed more frequently in whole patients with chronic cholecystitis. We also ascertained an outcome in that the conversion rate to open cholecystectomy was higher in the contracted GB group than in non-contracted GB group. It was previously reported that contraction of GB was the leading cause of conversion from laparoscopic cholecystectomy to open surgery due to obscure anatomy or increased risk of intraoperative complications. In summary, our study describes that biliary pain, the diffuse type of wall thickening and conversion to open cholecystectomy occurred more frequently in the contracted GB group. It suggests that contraction of GB, which resulted from long-standing chronic inflammation, is developed by more severe and more extensive damage of the GB wall than non-contracted cholecystitis is. Therefore, these results should be considered as the significant clinical factors that provide evidence for cholecystectomy in patients with contraction of GB.

In current study, we investigated the relationship between chronic cholecystitis with or without contraction of GB and incidental GB cancer. Distinguishing these two diseases from each other is a difficult problem. Both chronic cholecystitis and early GB cancer have no specific symptoms or findings, and imaging modalities such as ultrasonography and CT scan are inaccurate in determining the presence of early GB cancer. There have been reports of many cases in which GB cancer could not be diagnosed until the patient underwent cholecystectomy.

According to our data, seven patients (1.7%) received a final diagnosis of GB cancer among 409 patients. All of these GB cancer patients were older than 60 years of age and had undergone cholecystectomy due to biliary pain. It suggests that biliary pain is an important factor
cholecystectomy were higher in the contracted GB group. Incidental GB cancers were rarely diagnosed (1.7%), although chronic cholecystitis with or without contraction of GB was regarded as a precancerous lesion. All of the cancer patients were older than 60 years of age and had biliary pain. However, contraction of GB and the type of wall thickening were not related to GB cancers. Our results suggest that patients who have chronic cholecystitis, with or without contraction of GB, should be observed carefully if they do not complain of biliary pain, depending on the age and general condition. These will be used as significant evidences when making a decision regarding an observation or operation in chronic cholecystitis patients with or without contraction of GB.

요 약

배경/목적: 만성 담낭염이란 담낭의 만성적인 염증반응으로 인해 담낭벽의 비후를 보이는 질환으로 염증이 오랜 기간 지속되면서 담낭벽의 수축성 변화를 유발하기도 한다. 만성적인 만성 담낭염, 특히 담낭의 수축성 변화는 임상적 이행도 심한 증상, 하지만 만성 담낭염과 담낭벽의 수축성 변화에 대한 임상적인 의문을 살펴본 연구가 거의 없고 담낭암과의 관련성 또한 연구된 바가 없다.

방법: 본 연구에서는 복부초음파와 CT를 통해 만성 담낭염으로 진단된 환자 중 수술을 시행하여 조직학적 확인을 받은 409명의 환자를 분석하였다.

결과: 409명의 만성 담낭염 환자 중 94%에서 담석이 있었고, 25% 환자에서 수축성 담낭을 가지고 있었다. 담낭벽 수축성 변화 유무로 나누어 분석하였을 때 수축성 담낭과 동시에 복통을 호소하였던 환자가 많았고, 미만성 형태의 담낭벽 비후 및 계곡수술로 진단된 비율이 높았다. 409명의 환자 중 7명이 담낭암으로 최종 진단되었는데 모두 80세 이상의 고령이었고 담석성 복통을 호소하여 수술을 진행하였다. 담낭벽 비후 형태, 수축성 변화는 담낭암 환자에서 차이가 없었다.

결론: 담낭의 수측성 변화는 만성 담낭염의 심한 형태로 생각되나 담낭암을 예측하는 데 있어서 의미는 없었다. 따라서 수측성 변형의 유무와 죽장이 없는 만성 담낭염 환자에서는 고령이고 복통이 있으면 담낭절제술이 권고되지만 이런 조건에 맞지 않다면 수술의 감소 추천안도 고려해야 할 수 있었다.

국문 석인: 담낭, 담낭염, 담낭암
Clinical Significances of Chronic Cholecystitis

Conflicts of Interest

The author has no conflicts to disclose.

REFERENCES