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## Original research

## Cholesterolosis in routine histopathological examination after cholecystectomy: What should a surgeon behold in the reports?

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## HIGHLIGHTS

- Cholesterolosis is associated with metaplasia.
- There is no relation between age and increased gallbladder wall thickness.
- Gallbladder wall thickness is not correlated with presence of acute inflammation.
- Cholesterolosis is not correlated with acute inflammation and polypoid lesions.
- Routine histopathological examination is very important.

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## ABSTRACT

**Introduction:** Cholecystectomy is one of the most common surgical procedures. Postoperative investigation of cholecystectomy specimen has a great value since histopathological reports may document some entities with significant clinical consequences. The aim of this study was to evaluate the association between cholesterolosis and the reports indicating some histopathological alterations in symptomatic cholecystitis. **Methods:** This paper is based on a retrospective study. Histopathological reports of 432 cholecystectomy specimens between January 2011 and June 2013 were reviewed. Three reports were excluded due to perioperative diagnosis of cancer. Reports of 429 cholecystectomy specimens of the acute and symptomatic chronic cholecystitis patients were analyzed. Standardization of the reporting was questioned. Age, gender, histopathological wall thickness of gallbladder, reporting rates of acute inflammation, cholesterolosis, polypoid lesions, epithelial hyperplasia, gastric or intestinal metaplasia, dysplasia and incidental cancer were investigated and compared between patients with and without cholesterolosis. Reported rates of histopathological findings were comparable between patients under and over 60 years old and patients with and without reported cholesterolosis. **Results:** Reported histopathological findings were presented as acute inflammation in 46 (10.7%), cholesterolosis in 79 (18.4%), gallbladder polypoid lesions in 7 (1.6%), epithelial hyperplasia in 16 (3.7%), metaplasia of any type in 34 (7.9%) of 429 patients. Dysplasia was excluded whereas one incidental gallbladder carcinoma was reported. Epithelial hyperplasia and metaplasia were found to be related to age. Gallbladder wall thickness was decreased with cholesterolosis. However, only a correlation between cholesterolosis and gender or metaplasia was noted. **Conclusion:** Recent study suggests that cholesterolosis is somehow associated with metaplasia. Thus, surgeons should carefully interpret the histopathology reports based on unusual or exceptional findings corresponding to the cholecystectomy specimens. Any abnormal finding in the reports should be investigated in terms of the progress of the pathology and also its clinical consequences.

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## 1. Introduction

Cholecystectomy is a common surgical procedure which is performed routinely for several diseases of gallbladder including acute or chronic cholecystitis, polypoid lesions and cancer [1–4]. Preoperative imaging is essential not only for the diagnose of clinical conditions, but also for surgical planning. Ultrasonography is used primarily to evaluate gallbladder wall thickness and or morphological alterations [5], whereas some advanced diagnostic imaging techniques are used according to the existing clinical conditions [6,7]. However, routine histopathological examinations might be needed to confirm the diagnosis and to predefinition of some incidental findings such as cancer in the presence of inadequate or limited imaging techniques [8,9].

Transabdominal ultrasonography may be help to measure gallbladder thickness since a gallbladder wall thickness >3 mm is considered as a diagnostic characteristic of acute cholecystitis. Some other clinical conditions should be considered in the differential diagnosis in the early phase of the disease [10,11]. However, incidental or rare lesions such as true gallbladder polyps and even cancer was reported as might be misdiagnosed with ultrasonography [12]. Currently, an age-based ultrasonography protocol was suggested for designation of asymptomatic cholelithiasis and >60 years old patients were evaluated less likely to have acute cholecystitis [13]. Contrast enhanced endoscopic ultrasonography has been recently presented to improve diagnostic accuracy and to state an interobserver agreement in the differential diagnosis for patients with gallbladder thickening [14].

The diagnosis of an incidental cancer or a premalignant lesion should alert the clinician for further medical investigation and surgical intervention. It has been reported that some incidental lesions of the gallbladder may be observed or recognized during histopathological evaluation of the cholecystectomy specimen [15]. A metaplasia-dysplasia and cancer sequence has been interpreted from this perspective [16,17] and routine and selective histopathological evaluation of cholecystectomy according to several risk factors, such as age, was discussed previously [18]. Thus, it should be considered that routine histopathological evaluation and a standardized documentation may help the clinician to handle such complicated conditions in time.

Selective histopathological evaluation of cholecystectomy according to several risk factors, such as age should be questioned [18]. It is obvious that a selective approach may lead to a delay in diagnosis of cancer leading physicians to face with an advanced cancer patient will be hardly managed for medical cure. In addition, surgeons will be responsible for medico-legal issues.

The aim of the present study is to evaluate the reported cholesterolosis rates and its association with histopathological gallbladder wall thickness and other reported histopathological findings.

## 2. Materials and methods

### 2.1. Ethical issues

Institutional review was not required since this is a retrospective study.

### 2.2. Patient's issue

Histopathology records of the patients with acute and symptomatic chronic cholecystitis who were treated with open or

laparoscopic cholecystectomy at the dates of January 2011 and June 2013 were reviewed retrospectively. 432 records were included in the study. Perioperative diagnosis of gallbladder cancer was suspicious for three patients. These were confirmed to have adenocarcinoma and were excluded from the analysis. Age and gender were recorded for demographic analysis. The documentation concerning the preoperative ultrasonography performed routinely before cholecystectomy was not evaluated in the present study due to the lack of data standardization.

Reports concerning to the results of the routine histopathological examination following cholecystectomy with macroscopic morphometric measurements on three independent specimen samplings were evaluated using a standardized form including the headings of “age, gender, specimen site, specimen extraction method, basic clinical information, macroscopic findings and histopathological diagnosis”. However, histopathological reports did not include standardized information under the headings of basic clinical information, macroscopic findings and histopathological diagnosis. ICD codes were not included in the reports. Microscopic findings were not standardized, and relatively detailed reports of the patients diagnosed with cancer preoperatively were compared with the others. Thus, only gallbladder wall thickness and morphological parameters of cholecystectomy specimens were taken into consideration in this study since the other parameters were not reliable to be used as a data.

### 2.3. Study design

Two groups were included in the study: control group was comprised of the patients without cholesterolosis whereas study group consisted of those with cholesterolosis. Control and study groups were compared according to age, gender and histopathological parameters.

### 2.4. Histopathological parameters

Histopathological parameters included gallbladder wall thickness, reporting rates of cholesterolosis, polypoid lesions, acute inflammation, epithelial hyperplasia, gastric or intestinal metaplasia, dysplasia, and incidental cancer.

### 2.5. Statistical analysis

Case processing summary, age, gender, frequency and descriptive analysis were performed using SPSS version 13.0 (SPSS Inc, USA). Differences between study parameters such as age, gender, histopathological parameters, gallbladder wall thickness and other findings were analyzed using Chi-Square test. Mann–Whitney *U* test was used to compare the patients with and without cholesterolosis. Correlations between cholesterolosis and age, gender or other study parameters were tested with Pearson correlation test. Student *t* test was used to compare the patients ≤60 years and >60 years old age or with and without cholesterolosis for gallbladder wall thickness. Linear logistic regression analysis was used to evaluate the relation between age and gallbladder wall thickness. A power analysis was not performed. *p* < 0.05 was considered as statistically significant.

## 3. Results

Basic features and data obtained from 429 patients with acute or symptomatic cholecystitis in the case series are presented in Table 1. One patient with a right abdominal pain was diagnosed with incidental gallbladder carcinoma (signet cell carcinoma)

**Table 1**  
Basic features and findings of the study cohort.

Basic features	Finding
Sample Size	$n = 429^a$
Mean $\pm$ SD age [min–max]	$52.8 \pm 14.4$ [17–87]
$\leq 60$ years old aged patients	288/429 (67.1%)
$>60$ years old aged patients	141/429 (32.9%)
Female ratio	327/429 (76.2%)
Male ratio	141/429 (32.9%)
Gallbladder wall thickness (mm)	$2.6 \pm 14.4^b$
Incidental gallbladder cancer reporting rate	1/429 (0.2%) <sup>c</sup>
Polypoid lesion reporting rate	7/429 (1.6%)
Cholesterosis reporting rate	79/429 (18.4%)
Acute inflammation reporting rate	46/429 (10.7%)
Epithelial hyperplasia reporting rate	16/429
Gastric metaplasia reporting rate	25/429 (5.8%)
Intestinal metaplasia reporting rate	13/429 (3.0%)
Metaplasia reporting rate	34/429 (7.9%) <sup>d</sup>

<sup>a</sup> Three patients with perioperative diagnosis of gallbladder cancer were excluded from the analysis.

<sup>b</sup> reported histopathological measurements and values were used.

<sup>c</sup> thus overall gallbladder cancer rate is 4/432 (0.9%), and.

<sup>d</sup> in two patients type was not defined for metaplasia and in six patients both gastric and intestinal metaplasia were reported.

documented on the histopathological report. Millimetric gallbladder stones and increased wall thickness was documented on the ultrasound report of this patient and cholesterosis was not observed. In addition, upper and lower gastrointestinal endoscopic examination of the present patient was not significantly different from other patients. Advanced gallbladder adenocarcinoma was diagnosed in a patient having a previous ultrasonography report indicating increased gallbladder wall thickness. Perioperative tumoral gallbladder wall thickening were observed in two patients with increased gallbladder wall thickness. Diagnosis of adenocarcinoma was confirmed with histopathological examination.

Chi-square analysis documented significant differences for age, gender, histopathological parameters, gallbladder wall thickness and other findings between control and study groups. However, linear regression analysis excluded a relation between age and histopathological gallbladder wall thickness ( $p = 0.602$ ).

Reported histopathological findings in the patients  $\leq 60$  and  $>60$  years old are presented in Table 2. Reporting rates of epithelial hyperplasia, gastric metaplasia, intestinal metaplasia and metaplasia were significantly higher in the elderly patients. However, age was not correlated with histopathological gallbladder wall thickness and reported acute inflammation rates.

Reported histopathological findings in the patients with and without cholesterosis are presented in Table 3. Cholesterosis was positively correlated with female gender. However, it was not age related. Gallbladder wall thickness and reported metaplasia rates were lower in the patients with cholesterosis. However, acute inflammation, polypoid lesions and incidental cancer rates were not related to cholesterosis.

#### 4. Discussion

Cholesterosis of the gallbladder has been previously described as a different clinical clinically silent [19,20]. Ultrasonography and confirmation with histopathological examinations are recommended [21]. Recently, Ozgur et al. reported that increase in cases diagnosed as cholesterosis were positively correlated with increased sample size in cholecystectomies in a series of 432 patients with pathology records [22]. Authors compared the initial data obtained from two to three samples with the six new samples. Cholesterosis reporting rate was found to be 95 (22%) of 432

**Table 2**  
Comparison of the reported histopathological findings in  $\leq 60$  and  $>60$  years old patients.

	$\leq 60$ years old patients ( $n = 288$ )	$>60$ years old patients ( $n = 141$ )	$p$ value <sup>a,b,c</sup>
Gallbladder wall thickness (mm)	$2.6 \pm 1.0$	$2.7 \pm 1.1$	0.366 <sup>d</sup>
Acute inflammation reporting rate	26/288 (9.2%)	20 (14.2%)	0.105
Incidental cancer reporting rate	1/288 (0.3%)	–	0.484
Cholesterosis reporting rate	57/288 (19.8%)	13 (9.2%)	0.294
Polypoid lesion reporting rate	5/288 (1.7%)	22 (15.6%)	0.807
Epithelial hyperplasia reporting rate	3/288 (1.0%)	10 (7.1%)	0.000
Gastric metaplasia reporting rate	3/288 (1.0%)	28 (19.9%)	0.000
Intestinal metaplasia reporting rate	3/288 (1.0%)	2 (1.4%)	0.001
Metaplasia reporting rate	6/288 (2.1%)	22 (15.6%)	0.000

<sup>a</sup>  $p < 0.05$  was significant.

<sup>b</sup> Mann Whitney  $U$  test, and.

<sup>c</sup> correlation and linear regression analysis, and.

<sup>d</sup> Student  $t$  test were discussed in the text.

**Table 3**  
Comparison of the reported histopathological findings in cases with and without cholesterosis.

	Cholesterosis (–) ( $n = 350$ )	Cholesterosis (+) ( $n = 79$ )	$p$ value <sup>a,b,c</sup>
Gallbladder wall thickness <sup>d</sup> (mm)	$2.7 \pm 1.1$	$2.4 \pm 1.0$	0.049 <sup>d</sup>
Acute inflammation rate	34	12	0.156
Incidental cancer rate	1	–	0.635
Polypoid lesion rate	6	1	0.777
Epithelial hyperplasia rate	15	1	0.201
Gastric metaplasia rate	23	2	0.167
Intestinal metaplasia rate	12	–	0.082
Metaplasia rate <sup>d</sup>	32	2	0.050 <sup>d</sup>

<sup>a</sup>  $p < 0.05$  was significant.

<sup>b</sup> Mann Whitney  $U$  test, and.

<sup>c</sup> Correlation and linear regression analysis, and.

<sup>d</sup> Student  $t$  test were discussed in the text.

patients with routine sample size while increased sample size improved the cholesterosis reporting rate to 108 (25%) ( $p > 0.05$ ). Cholecystitis and dysplasia rates were not altered. Increasing the sample size enhanced the possibility of diagnosis of metaplasia and polyps. This result indicates a necessity for further detailed study for clarifying the significance of cholesterosis in routine histopathological sampling and examination. In our study, cholesterosis reporting rate was found to be 78 (19%) in 430 patients. This difference may be related to the laboratory sampling and processing techniques and also discrepancies in interpreting and reporting techniques. An interdisciplinary approach will help both surgeons and pathologists to improve these issues.

Increased gallbladder wall thickness with ultrasonography ( $>3$  mm) is considered to be related with acute cholecystitis and other lesions of the gallbladder. Age based protocol was previously presented by West W et al. [13]. The authors concluded that acute cholecystitis was less common in elderly patients ( $>60$  years old) with cholelithiasis. In our study, no correlation was found between age and increased gallbladder wall thickness. However, such correlation was previously reported for acute inflammation rates in

cholecystectomy specimens. This finding merits a prospective study to evaluate the correlation between ultrasonography and histopathological measurements of gallbladder wall thickness. In the present study, we observed no correlation between increased histopathological gallbladder wall thicknesses and the presence of acute inflammation in histopathological evaluation. This issue should be questioned and prompt surgeons to review the indication for gallbladder surgery after histopathological evaluation and documentation. This approach has potential to improve patient management.

The primary limitation of this study was the inadequacy in its retrospective design. Standardization and documentation should be improved with the aid of an interdisciplinary approach.

Acute cholecystitis is a common surgical disease which is relevant with increased gallbladder wall thicknesses with ultrasonography. It may be developed due to gallbladder stones (acute calculous cholecystitis). However, acute cholecystitis without documented gallbladder stones has been previously reported mostly in pregnancy and also in critically ill patients [23–25].

Cystic duct obstruction and bacterial invasion of gallbladder from other sources, bacterial translocation or systemic origin may be responsible in the development of most acute cholecystitis cases [26,27]. No correlation was detected between cholesterolosis and acute inflammation in this study. This finding should be evaluated by considering the other pathophysiological theories for acute cholecystitis in the absence of gallbladder stones.

We observed an association between cholesterolosis and polypoid lesions. Polypoid lesions of the gallbladder with premalignant features was not reported. However, macroscopic measurements of the polypoid lesions have been not documented. True polypoid lesions of gallbladder were previously reported [28,29]. It is common to recognize polypoid lesions >1 cm with ultrasonography and true polyps may be relevant with other histopathological changes [30–33]. True polyps are reported to be related with cancer [34]. In this study, no correlation was found between polypoid lesions and acute inflammation, epithelial hyperplasia and gastric or intestinal metaplasia suggesting that there may be an internal error which is not resulted from our study protocol. Thus, presence of a polypoid lesion with preoperative ultrasonography should alert surgeon and pathologist to examine the presence of true epithelial polyps and relevant cellular alterations in cholecystectomy specimens.

## 5. Conclusion

The results of this study indicate that cholesterolosis is somehow associated with metaplasia; however, it is not correlated with the other histopathological changes. Thus, surgeons should carefully interpret the reports based on unusual or exceptional findings corresponding to the cholecystectomy specimens. Any abnormal finding in the reports should be investigated in terms of the progress of the pathology and also its clinical consequences. These findings suggest that in general an interdisciplinary approach to cholecystectomy candidates, especially routine histopathological examination and standardization of both histopathology and ultrasound reports, is very important for the benefit of the patients.

## Ethical approval

This is a retrospective study. Thus institutional review was not required. The analysis in this article does not involve any new studies of human subjects performed by any of the authors. In addition, patient identifying information is not included in the study.

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## Author contribution

Please specify the contribution of each author to the paper, e.g. study design, data collections, data analysis and writing.

Faik Yaylak: study design, data analysis, literature search, drafting.

Aysenur Deger: data collection.

Bercis İmge Ucar: study design, data analysis, literature search, drafting.

Yalcin Sonmez: data collection.

Zulfu Bayhan: data collection.

Fahri Yetisir: study design, data analysis, literature search, drafting.

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## Conflicts of interest

All authors have declared that they have no conflict of interest.

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The present study is a retrospective one which does not involve any investigation on human or animal subjects. Patient identifying information is not included in the study.

We declare that the authors met the ICMJE criteria for authorship for this manuscript, took responsibility for the integrity of the work as a whole, and approved the final version to be published. The authors have no conflict of interest. Mehmet Fatih Ekici, Mustafa Cem Algin, and Cengiz Kocak are acknowledged for supporting the data collection.

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