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Assessment of Gallbladder Epithelial Lesions and Clinicopathological High-Risk Patient

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Abstract

Objective

Recognizing epithelial pathologies in the gallbladder and understanding the accompanying clinicopathological features may be useful in determining the decision for cholecystectomy. However, this distinctive selection in gallbladder patients has not been fully elucidated yet. In our series, we aimed to investigate the relationship between epithelial pathologies of the mucosa and clinicopathological findings in cholecystectomy materials and evaluate them in the light of the literature.

Material and Methods

We designed a retrospective cross-sectional study in which we re-evaluated Hematoxylin & Eosin-stained slides of 852 cholecystectomy materials operated in our hospital for two years. Mucosal pathologies were grouped as papillary hyperplasia (PH), pyloric metaplasia (PM), intestinal metaplasia (IM), epithelial dysplasia (ED), and cancer. We obtained the demographic data from the electronic archive system of our hospital. The chi-square test and Fisher's exact test were used, and p <0.05 was considered significant.

Results

The mean age of the patient was 53.17 ± 13.48. PH, PM, IM, PM+IM, ED, and invasive cancer were detected in 11.38%, 8.92%, 11.15%, 07.04%, 3.16%, and 0.47% of all cases, respectively. The mucosal pathologies were mostly observed over 50 years (p <0,05). The mass-forming lesion could not be detected among dysplasia cases (p <0.0001).

Conclusion

Age was found to be an essential factor for gallbladder epithelial changes in our study. We argue that taking additional macroscopic samples would be more effective in the definitive diagnosis of gallbladder epithelial pathologies in this age group, and being more careful when deciding on the indication for cholecystectomy in the over-50 age group.

Keywords: Gallbladder, Mucosal pathologies, Cholecystectomy, Diagnosis, Demographic findings

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Introduction

Cholecystectomy is one of the most commonly encountered procedures in routine surgical pathology practice. The primary clinical indication for cholecystectomy is cholelithiasis. However, a broad spectrum of mucosal pathologies, ranging from chronic inflammation and metaplasia to intraepithelial neoplasia and even carcinoma, can be incidentally identified during routine histopathological evaluation. While these epithelial changes are typically identified on hematoxylin and eosin-stained sections, additional diagnostic techniques may be required in suspicious cases. Before histopathological diagnosis, clinical and demographic data alone are insufficient for accurately classifying patients at risk for epithelial lesions. Therefore, a detailed histopathological examination of cholecystectomy specimens is essential to identify, characterize, and define these patient groups.

Over the past 20 years, epithelial changes in the gallbladder have received significant attention. While numerous clinical and etiological factors, such as age, gender, cholelithiasis, and inflammatory processes, have been proposed to influence epithelial changes, many of these associations remain controversial (1–4). In addition to established criteria for patient selection for cholecystectomy, it is crucial to define the clinicopathological features associated with mucosal pathologies of the gallbladder. Enhancing the macroscopic evaluation of cholecystectomy specimens by increasing the number of tissue samples examined is an effective approach for identifying these pathologies (3,5).

This study aims to investigate the relationship between mucosal pathologies in cholecystectomy specimens and associated clinicopathological findings.

Material and Method

Patients' Characteristics and Histopathological Features

This study included 896 cholecystectomy specimens submitted to the clinical pathology department of Buca Seyfi Demirsoy Education and Research Hospital between January 1, 2023, and the end of September 30, 2024. Clinical, pathological, and demographic data of all patients were retrieved from the pathology department's electronic database, and H&E sections were reevaluated. Cases were excluded if paraffin blocks or Hematoxylin and Eosin (H&E)-stained slides were unavailable in the pathology archive or if macroscopic data were incomplete. As a result, we examined 852 patient specimens.

The macroscopic evaluation in our laboratory followed a standardized procedure. For all cholecystectomy specimens without a preoperative diagnosis of malignancy, six samples were taken from the surgical neck margin, fundus, and corpus for routine assessment as two paraffin blocks. If epithelial dysplasia was identified during the initial microscopic examination, the specimen was re-evaluated macroscopically, and additional samples were taken. This approach has been taken as suggested by Roa et al. (6). This additional sampling was not routinely performed for cases with metaplasia.

Without knowing the clinical data, the pathologist reviewed all H&E-stained slides using light microscopy for this study under the current literature (6). Mucosal pathologies were classified as papillary hyperplasia (PH), pyloric metaplasia (PM), intestinal metaplasia (IM), low- and high-grade intraepithelial neoplasia, or invasive carcinoma. Cases presenting both low- and high-grade dysplasia were categorized as epithelial dysplasia. The presence and absence of pathological lesions in the table were evaluated as present or absent as a result of histopathologic examination, and were not further categorized. Macroscopic findings were categorized based on the presence or absence of stones and mass-forming lesions (exophytic masses ≥ 0.2 cm). Histological findings were similarly classified for the presence or absence of acute and chronic inflammation. Clinical, demographic, and macroscopic data were retrieved from the hospital's archival records.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics v21.0. The association between demographic features and mucosal pathological characteristics was assessed using the chi-square test. Fisher's exact test was applied for comparisons of categorical variables. A p-value <0.05 was considered statistically significant in all analyses.

Results

Firstly, we evaluated the similarities between the selected and excluded case groups to exclude the selection bias. We had a result that the 44 cases excluded had similar demographic and pathological data, and did not affect the general demographic characteristics of the selected case group.

The mean age of the patients was 53.17 ± 13.48 years, and 80.04% were women. Macroscopic examination revealed cholelithiasis in 745 cases (87.44%) and mass-forming lesions in 45 cases (5.28%). Mucosal pathologies were observed in 359 cases (42.13%).

Table 1 The distribution of current histopathological features according to age and gender

	Age		P value	Gender		P value
	50	≥50		F	M	
Papillary hyperplasia	43 (44.33%)	54 (55.67%)	**0.001**	77 (79.38%)	20 (20.62%)	**0.160**
Pyloric metaplasia	29 (38.16%)	47 (61.84%)		61 (80.26%)	15 (19.74%)	
Intestinal metaplasia	20 (21.05%)	75 (73.96%)		83 (87.36%)	12 (12.64%)	
Epithelial dysplasia	5 (18.52%)	22 (81.48%)		22 (81.48%)	5 (18.52%)	
Pyloric and Intestinal metaplasia	11 (18.33%)	49 (81.67%)		52 (86.67%)	8 (13.33%)	
Invasive carcinoma	0 (00.00%)	4 (100.0%)		4 (100.0%)	0 (00.00%)	
Cholelithiasis	307 (41.21%)	438 (58.79%)	**0.503**	595 (79.86%)	145 (20.14%)	**0.398**
Mass-form lesions	19 (42.33%)	26 (57.77%)	**0.856**	40 (88.89%)	5 (11.11%)	**0.120**
Acute inflammation	60 (36.13%)	90 (63.87%)	**0.196**	101 (67.33%)	49 (32.66%)	**0.072**
Chronic inflammation	349 (41.95%)	483 (58.05%)	**0.713**	651 (78.25%)	181 (21.75%)	**0.506**

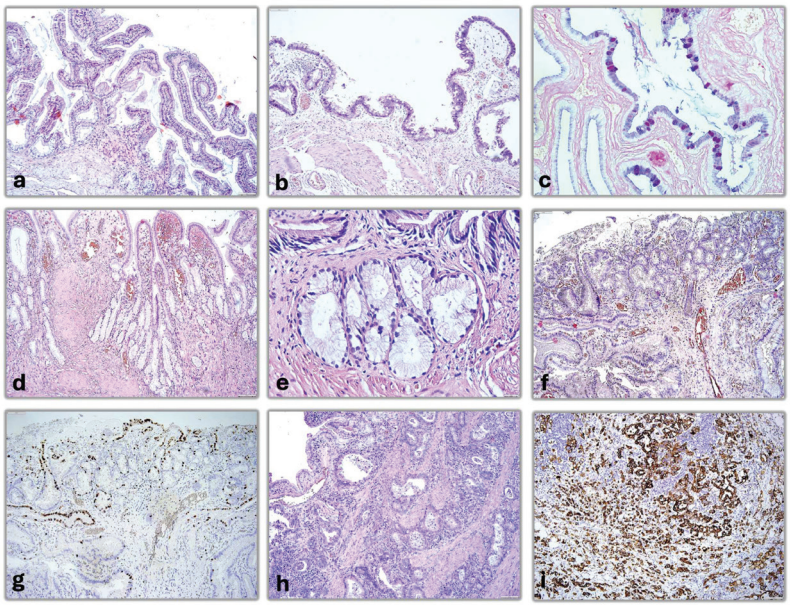

Figure 1
The histomorphological features of gallbladder mucosal lesions a) Papillary hyperplasia (PH), (Hematoxylin&Eosin) H&E, x10; b-c) Intestinal metaplasia (IM), H&E (b) and (Periodic acid schiff-alcian blue) PAS+AB histochemical staining (c), x10; d, e) Ploric metaplasia (PM), H&E, x10 (d) and X40 (e); f-g) Low-grade epithelial dysplasia, H&E (f) and Ki-67 proliferation index immunohistochemical staining (g), x10; h-i) Invasive adenocarcinoma, H&E (h), and Cytokeratin 7 (CK7) immunohistochemical staining (i) x20.

Among these, papillary hyperplasia (PH) was identified in 97 cases (11.38%) (Figure a), pyloric metaplasia (PM) in 76 cases (8.92%) (Figures d-e), intestinal metaplasia (IM) in 95 cases (11.15%) (Figures c,d), PM+IM in 60 cases (07.04%), low-grade dysplasia in 27 cases (3.16%) (Figures f-g), and invasive carcinoma in 4 cases (0.47%) (Figures h-i). None of the patients had high-grade dysplasia as an isolated finding; all cases of high-grade dysplasia were observed in the mucosa adjacent to invasive carcinoma.

Relationship Between Age and Mucosal Pathologies

A majority of patients with mucosal pathologies were older than 50 years. Specifically, 54 (55.67%) of patients with PH, 47 (61.84%) with PM, 75 (73.96%) with IM, 49 (81.67%) with PM+IM, 22 (81.48%) with epithelial dysplasia, and all four patients with carcinoma (100%) were over 50 years of age. A statistically significant association was found between the presence of mucosal pathologies and age ($p = 0.001$) (Table).

Relationship Between Gender and Mucosal Pathologies

Among the patients with mucosal pathologies, 77 (79.38%) of 97 with PH, 61 (80.26%) of 76 with PM, 83 (87.36%) of 95 with IM, 52 (86.67%) of 60 with PM+IM and 22 (81.48%) of 27 with dysplasia, all Invasive carcinoma (4 (100.0%)) were women. However, no statistically significant relationship was found between gender and the occurrence of PH ($p = 0.697$), PM ($p = 0.211$), IM ($p = 0.332$), PM+IM ($p = 0.282$), or dysplasia ($p = 0.408$). All four carcinoma cases occurred in women. However, this finding was insufficient for statistical analysis due to the limited number of carcinoma cases. Furthermore, when dysplasia and carcinoma were analyzed as a single group, no significant relationship was detected between gender and dysplastic changes ($p = 0.408$). The distribution of histopathological features and mucosal pathologies across all cholecystectomy specimens is summarized in the Table.

Relationship Between Macroscopic Features and Mucosal Pathologies

Cholelithiasis was identified in 80.2% of patients with PH, 84.9% with PM, 60% with IM, 88% with PM+IM, 78.6% with dysplasia, and 100% with carcinoma. However, no statistically significant relationship was found between cholelithiasis and mucosal pathologies, including PH ($p = 0.404$), PM ($p = 0.125$), IM ($p = 0.194$), PM+IM ($p = 0.204$), dysplasia ($p = 0.371$), and carcinoma ($p = 0.482$).

A total of 45 cases exhibited macroscopic mass-forming lesions, of which 26 (57.77%) were cholesterol polyps, 7 (15.55%) were PM, 2 (4.44%) were IM, 6 (13.33%) were PH, and 4 (8.88%) were invasive carcinoma. No macroscopic mass-forming lesion was observed in epithelial dysplasia cases. While no significant relationship was found between mass-forming lesions and PH ($p = 0.726$) or PM ($p = 0.791$), it was significant that none of the patients with dysplasia had a mass-forming lesion ($p < 0.0001$).

Relationship Between Mucosal Pathologies

Chronic inflammatory infiltration was more common than acute inflammation in patients with PH ($p = 0.026$) and dysplasia ($p = 0.001$).

Among the 97 patients with PH, 21 also had metaplasia, with 19 of these cases exhibiting PM and 2 showing IM. One patient with both PH and IM also had carcinoma. Invasive carcinoma was not observed in any patient with PM, whereas two patients with IM were diagnosed with carcinoma. Due to the limited number of cases with these mucosal pathologies, statistical analysis was not applied to these findings.

Discussion

Cholecystectomy is one of the most commonly performed procedures in general surgery. For instance, approximately 750,000 cholecystectomies are conducted annually in the United States (7), 25,000 in the Netherlands (8), and an estimated 40,000–60,000 in Turkey (9). There is ongoing debate regarding the necessity of routine histopathological examination for cholecystectomy specimens that lack visible macroscopic pathology. Nonetheless, the widely accepted view is that routine histopathological evaluation should be performed on all cholecystectomy specimens (9–12). This recommendation stems from the fact that gallbladder tumors do not always form easily noticeable masses, and most cancers cannot be detected through clinical or radiological methods. Furthermore, it is well-documented that a small proportion of gallbladder tumors develop without forming a visible mass and are only incidentally discovered during histopathological examination (13–16). Benign epithelial metaplastic changes and low- or high-grade intraepithelial dysplasia in the gallbladder typically do not produce mass-forming lesions, making incidental detection during pathological evaluation crucial (9). In our study, we detected two cases of invasive tumors penetrating the muscle layer of the gallbladder (pT1 b according to WHO 2019) incidentally. The reported rate of incidental tumors in the literature is 0.15%–0.3 %, consistent with our 0.46% findings (13,14,16). Additionally, epithelial dysplasia cases, like the two cancer cases we identified, showed no

evidence of macroscopic mass lesions. These results further support routine histopathological examination of cholecystectomy specimens, as advocated in the literature (10–12,17,18).

The molecular mechanism of subsequent epithelial changes along the line of malignancy is not clear, because diagnosis can be generally obtained incidentally (6,19,20). Some molecular pathway abnormalities can be detected to this day, such as the mucin family members and the P53 pathways (6,18–20).

A thorough macroscopic evaluation is essential to identify premalignant or malignant lesions that do not form masses. Additional sections must be taken if suspicious epithelial abnormalities are detected during the initial histopathological examination. This step is critical, as additional sampling can reveal carcinoma. Consequently, pathologists must be aware of patient groups at higher risk for gallbladder epithelial lesions to detect accompanying malignancies or associated mucosal pathologies, because not all samples can be subjected to extensive examination during routine pathology examination.

Papillary hyperplasia (PH) in the gallbladder is categorized as either primary or secondary. Epithelial dysplasia is more likely to develop in the context of secondary PH, which is often associated with chronic cholecystitis, adenomatous hyperplasia, or other inflammatory conditions (21). However, there is limited evidence in the literature to confirm this relationship. In our study, chronic inflammation was present in 93.8% of PH cases, suggesting that most of our cases were secondary PH. However, only two cases of PH were associated with low-grade intraepithelial neoplasia, and three cases were associated with intestinal metaplasia (IM). No statistically significant relationship was found between PH and dysplasia or metaplasia.

When comparing our findings on PH to the existing literature, we found limited information and no established diagnostic criteria for PH. This lack of standardization may make it challenging for pathologists to identify PH consistently. Additionally, the malignant potential of PH remains unclear in the current literature. Larger case studies involving PH are needed to clarify diagnostic criteria and establish a standardized macroscopic approach for evaluating these lesions.

The most common pathological diagnoses in cholecystectomy specimens are cholelithiasis and chronic cholecystitis. Chronic cholecystitis is diagnosed based on morphological criteria such as dominant mononuclear cell infiltration, fibrosis, and, in some cases, metaplastic changes (21). Chronic inflammation can be a key factor in the development of metaplastic changes in the gallbladder. In our study, 231 out of 832 cases with chronic inflammation demonstrated metaplastic changes. Pyloric metaplasia (PM) was the most common type of metaplasia observed in our study, which is consistent with the literature. While PM is less frequently associated with precancerous potential, intestinal metaplasia (IM) has a much stronger link to cancer. In our study, low-grade dysplasia was observed in 8.66% of PM cases but in 28% of IM cases (17). Notably, IM was observed in the mucosa adjacent to invasive cancer in two cases, further supporting the association between IM and cancer despite the small number of cases (17).

Akki et al. suggested that when cholecystectomy specimens contain IM or dysplasia, the entire gallbladder should be examined histopathologically (22). They also recommended additional sampling for patients with low-grade dysplasia, although this was deemed unnecessary for cases with IM. In contrast, Adsay et al. argued that two additional samples should be taken in cases of IM (5). In our study, additional sections were obtained for cases with epithelial dysplasia and IM. The relatively low rates of low-grade dysplasia in our study may be attributed to the lack of additional sampling. Our findings, consistent with those of Esendağlı, Adsay, and Akki et al., underscore the importance of additional sampling in cases with epithelial changes (5,9,22).

The most common indication for cholecystectomy is cholelithiasis (3,8). Gracia and Ransohoff followed 123 patients with asymptomatic gallstones for over ten years and found that none developed cancer (23). However, other studies have reported a strong association between gallstones and gallbladder cancer (3,7,24,25). In our study, 80.24% of PH cases, 60% of IM cases, 78.57% of dysplasia cases, and all cancer cases were associated with cholelithiasis. However, no statistically significant relationship was found between the presence of gallstones and mucosal pathologies. Metaplasia, dysplasia, and cancer were observed more frequently in our group over 50 years of age, and this finding was statistically significant. These data are consistent with the literature, and we think age should be considered before cholecystectomy.

One study investigating the relationship between the demographic characteristics of gallstones (such as size, family history, and duration of stone presence) and cancer development showed that these factors

might contribute to cancer risk (26). While gallstones are believed to increase the incidence of cancer, most individuals with cholelithiasis do not develop gallbladder cancer in their lifetime (21). Although all cancer cases in our study were associated with cholelithiasis, the small sample size and lack of demographic data on gallstones limit the scope of our conclusions. Further large-scale studies are needed to investigate the potential effects of gallstones on the gallbladder mucosa and their relationship with mucosal changes, incorporating demographic characteristics for a more comprehensive understanding.

Gallbladder diseases are more prevalent in women, with the incidence reportedly increasing after the age of 50 (2,21,27,28). In our study, we also observed a predominance of female patients. However, statistical analysis did not reveal a significant relationship between female gender and mucosal pathologies. Our findings support existing literature indicating that female gender alone is not a determinant for cholecystectomy and does not necessitate changes in macroscopic evaluation methods (2–4,21,28).

Metaplasia, dysplasia, and cancer were observed more frequently in patients over the age of 50 in our study, a statistically significant finding. This aligns with previous reports, suggesting that age is a critical factor to consider before recommending cholecystectomy. Since mucosal pathologies and some cancers often do not form easily visible macroscopic masses, we propose that cholecystectomy specimens from patients over 50 years of age should be sampled more extensively during histopathological examination. Conversely, given that more than half of the patients in our study were over the age of 50, routinely increasing the number of samples for all such cases may not be economical or practical, particularly as even routine histopathological examinations for every cholecystectomy specimen are debated in the literature (15,16,27), but our results prove otherwise.

Although our study has a large population, it is limited to the comparisons between dysplasia and cancer because the number of these lesions is small and limited in this population. Additional studies are needed to compare the prevalence and distribution of epithelial dysplasia in the larger population. Since imaging methods are limited in detecting this type of epithelial lesion of the gallbladder, it is not possible to plan a prospective study at present. In this regard, our findings suggest that a more careful decision for cholecystectomy, including cancer markers, in patients over 50 years of age, may enable the future determination of risky patients.

It is claimed that if high-grade dysplasia is detected anywhere in the cholecystectomy specimen and the surgical margins are positive, the remaining part of the bile duct may be at risk for cancer development (18). These patients should be under close clinical follow-up. In conclusion, patient age should be considered not only when determining the indication for cholecystectomy but also during macroscopic pathological examination. For example, for patients over 50 years old, a more meticulous macroscopic evaluation and more extensive sampling of the gallbladder can be recommended, or the option of examining the entire cholecystectomy material may be considered, as done by Koshiol et al. (20).

In summary, based on the results of our study and the existing literature, further studies involving larger cohorts are needed to elucidate the stone-mucosal damage-cancer pathway.

Epithelial changes and cancer are more commonly detected in patients over 50 years of age. This demographic factor must be taken into account when determining cholecystectomy indications and during macroscopic pathological evaluation.

Conflict of Interest Statement
The authors declare no conflicts of interest regarding this article's research, authorship, or publication. The paper’s content and writing are solely the authors’ responsibility.

Ethical Approval
The Ethics Committee of the University of Izmir Democracy, Buca Seyfi Demirsoy Education and Research Hospital approved using primary tissue samples in this study (Reference Number: 2024/348, Date: December 30, 2024). This study adhered to the principles of the Helsinki Declaration and its subsequent amendments.

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Data available on reasonable request from the authors.

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The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

Authors Contributions

OO: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Validation; Visualization; Writing-original draft.

AI: Data curation; Formal analysis; Investigation; Validation.

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