# STANDARDIZED HISTOLOGICAL REPORTING OF CHOLECYSTECTOMIES FOR CHRONIC CHOLECYSTITIS; IS IT VALID?

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## ABSTRACT

**Objectives**: The objective of the study was to standardize a reporting system for histological examination of chronic inflammatory patterns in surgically resected gall bladder specimens and to emphasize the importance of this detailed examination.

**Materials and Methods:** Total numbers of cases included in this study were 450 who had their cholecystectomies done for chronic cholecystitis. Representative sections were taken from each specimen and processed routinely. Histopathologist examined H & E stained slides. The histopathological findings were recorded in accordance with a uniform checklist and scored according to laid down criteria.

**Results:** 342 specimens were from female patients and 108 specimens were from males. Their ages ranged from 16 to 86 years. 60% presented with chronic cholecystitis with cholelithiasis and in 40% of cases there were no gallstones. Mucosal hyperplasia was observed in 76% of cases. Inflammatory mononuclear cells infiltrate was present in all specimens and inflammatory activity was seen in 47% of the cases. 50% cases had metaplastic epithelium, dysplasia in 5.6% and carcinoma in 0.44% of cases.

**Conclusion:** It is concluded that this approach will provide a rational, systematic and reproducible diagnosis to the clinician so that they can have an accurate idea of the magnitude of the disease or any potential for simultaneous complications.

**Key Words:** Chronic cholecystitis, cholecystectomy, metaplasia

## INTRODUCTION

Gallbladder is one of the organs having a wide spectrum of diseases ranging from congenital anomalies, calculi and its complications, non-inflammatory, inflammatory and the neoplastic lesions[1]. It is one of the most usual sites for stones to occur which are a major cause of morbidity and mortality throughout the world[2]. 10% of the adult patients have asymptomatic gall stones[3]. There has been a significant increase in the gallstones disease as measured by ultrasonography and autopsy surveys[4]. Gall stones formation results from many complex factors working together. Among them, the bile stasis caused by impaired gall bladder emptying is thought to be the fundamental kinetic factor[3,5]. Chronic cholecystitis is virtually always associated with cholelithiasis i.e. 95% of cases and is the most common pathologic finding in the surgically resected specimens[6]. Pathology of this common disorder is poorly understood but it has been suggested that chronic cholecystitis occurs as a result of mild recurrent attacks of Acute Cholecystitis. The inflammatory and reparative changes may be in part explained by repetitive mucosal trauma

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produced by gallstones[5,7]. However, gallstones could not be solely held responsible, as 70-80% of patients having cholelithiasis are asymptomatic. Other factors like higher concentration of cholesterol in bile, presence of bile resistant H.pylori, E.coli or Giardia lambia just above the surface epithelium, Salmonella typhi in the gall bladders of chronic carriers and finally impaired gall bladder function are also implicated as causative agents for chronic cholecystitis[8].

The clinical diagnosis of chronic cholecystitis (CCH) is generally verified by biopsy. It involves numerous and variable morphological findings, ranging from minimal to gross alterations in the gallbladder structure[9]. Customarily the gall bladder specimens are quickly observed sent to the residents or junior pathologists and reported superficially[10]. It is observed with concern that the diagnostic terms such as acute and chronic cholecystitis, which is commonly being used in the of reporting such specimens, do not give an accurate idea of magnitude of disease or its potential for simultaneous complications[11]. For instance the degree of inflammation and activity shows a spectrum of histopathological changes in different layers of gall bladder wall. So the pathologist has to add a summarized description of the findings in a large perspective to have a greater impact on the future prospects of the patient[11,12]. The role of pathologist is to provide information regarding the inflammatory process and:

- Give a name to it i.e. acute or chronic cholecystitis
- Establish the presence of gall stones and its nature
- Describe the presence of associated changes, and
- Search for the presence of incidental carcinoma

In view of the above, there was a need for standardized diagnostic terminology for comprehensive microscopic reporting just like the knodell scoring system for hepatitis and the Sydney system for reporting gastritis[9,11,13]. There is general consensus that examination of a single tissue block with three sections of tissue to include the cystic duct margin represents the best balance between the necessities on the one hand to identify as many cases with significant pathology as possible[14]. In the present study we analyzed cholecystectomy specimens to provide a standardized diagnostic terminology based on objective and reproducible observations that would serve the clinical management in a better way.

## MATERIALS AND METHODS

A non-interventional descriptive study was conducted in order to device a quantitative methodology for reporting gall bladder specimens with the diagnosis of chronic cholecystitis, in accordance to standard parameters. The study population comprised of both male and female patients who underwent cholecystectomy and their gall bladders were sent to the Histopathology department of Hayatabad Medical Complex Peshawar and Armed forces Institute of Pathology Rawalpindi over a period of two years. Total number of specimens included in the study were four hundred and fifty (n=450). The study was conducted from May 2011 to May 2014. Those cholecystectomies were excluded from the studies which were diagnosed;

- Pre-operatively by the clinician as malignant, either primary or secondary, by the ultrasound or any diagnostic technique.
- Intra-operatively by the surgeon as having primary or metastatic tumor.

A detailed gross examination of gall bladder was done by opening length wise through the serosal lined surface. Longitudinal size, perimeter and wall thickness was recorded. Number, size and appearance of calculi were also recorded. Three samples were taken from the fundus, middle third and neck of gall bladder. The specimens were then routinely processed, embedded and stained with hematoxylin and eosin and were examined microscopically by two Histopathologists. An Olympus CH20 microscope with 10x/18L eyepieces and 40x/0.65 objective was used for this purpose.

### *RECORD KEEPING*

A proforma was prepared, which was used for every case. It included name, age, gender of the patient, presence or absence of gallstones and the histopathological findings in accordance with the following uniform criteria.

1. Metaplastic epithelium.

1. Present.
2. Absent.

2. Degree of inflammatory infiltrate.

a. Mild: Not more than 10 inflammatory cells / HPF in any layer.

b. Moderate: Between 11-30 cells/HPF.

c. Severe: More than 31 cells/HPF.

3. Inflammatory activity:

It is considered when one or more of these changes are present:-

a. Mild:

i. Vascular congestion

ii. Mild Neutrophilic infiltrate

b. Moderate

i. Vascular congestion

ii. Moderate Neutrophilic infiltrate

iii. Mucosal epithelial permeation (R.A.S)

c. Severe

i. Vascular congestion

ii. Marked Neutrophilic infiltrate

iii. Mucosal epithelial permeation (R.A.S)

4. Degree of mucosal hyperplasia

a. Present

b. Absent

5. Dysplasia

a. Present

b. Absent

6. Carcinoma

a. Present

b. Absent

7. Gall Stones

a. Present

b. Abs

## RESULTS

In the present study we analyzed a total of 450 cases of chronic cholecystitis that had undergone cholecystectomy. All the specimens were analyzed in

**Table 1.**

| S.No | | | |
|---|---|---|---|
| 1. | Gall stones | Present 270(60%) | Absent 180(40%) |
| 2.. | Mucosal Hyperplasia | Focal 176(39%) | Diffuse 166(37%) |
| 3. | Carcinoma | Present 2(0.44%) | Absent 449(99.6 %) |

**Table 2.**

| S.No | | Mild | Moderate | Severe |
|---|---|---|---|---|
| 1. | Inflammatory infiltrate | 90(20%) | 153(34%) | 207(46%) |
| 2. | Inflammatory activity | 95(21%) | 144(32%) | 221(47%) |
| 3. | Degree of fibrosis | 243(54%) | 171(38%) | 36(8%) |
| 4. | Dysplasia | 14(3.1%) | 8(1.7%) | 3(0.4%) |

**Table 3. Type of Metaplasia**

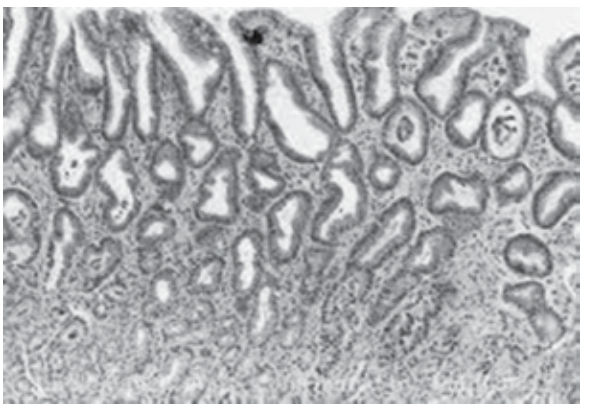
| Total | 225(50%) |
|---|---|
| Pyloric | 202(45%) |
| Intestinal | 16(3.5%) |
| Squamous | 7(1.5%) |

**Table 4. Co existing epithelial changes in the same section**

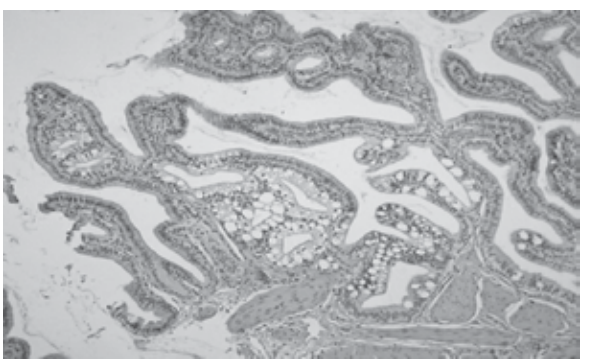
| S.No | Epithelial changes | Number of cases |
|---|---|---|
| 1. | Hyperplasia & Pyloric metaplasia | 24(5.3%) |
| 2. | Hyperplasia & Intestinal metaplasia | 8(1.7%) |
| 3. | Hyperplasia & Dysplasia | 17(3.7%) |
| 4. | Intestinal metaplasia, Dysplasia & Carcinoma | 1(0.2%) |

accordance to the devised proforma. The advantage gained was that, not even a minor detail of the specimen was missed. 342 specimens belonged to female patients and 108 specimens belonged to male patients. Their ages ranged between 16-86 years (mean 45.38 yrs). 270 cases presented with cholelithiasis and 180 cases had acalculus cholecystitis. Following were the observations made:-

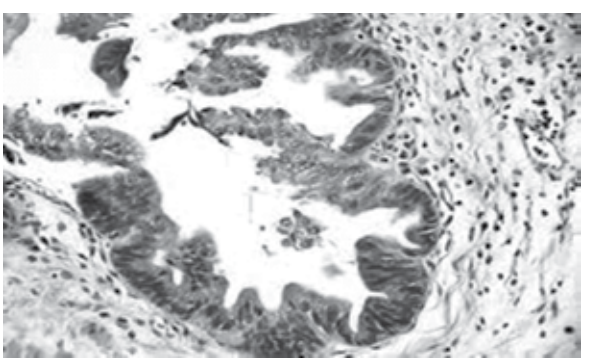
Mucosal Hyperplasia



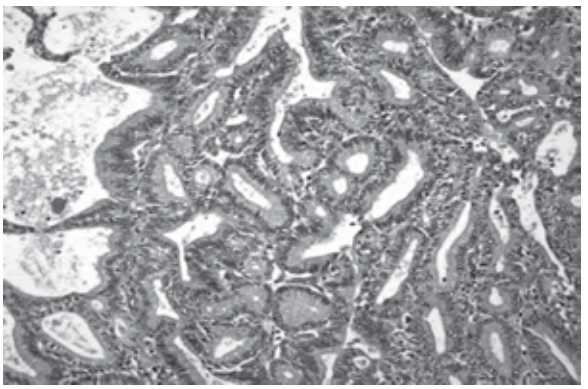
Pyloric Metaplasia



Intestinal Metaplasia



Carcinoma In Situ



Adenocarcinoma

1. Inflammatory mononuclear cells infiltrate was present in all specimens, which was mild in 20%, moderate in 34% and severe in 46% of cases.
2. Activity was present in 47% of the cases with severe activity, 32% with moderate activity and 21% with mild activity.
3. Mucosal hyperplasia was observed in 76% of cases of which 39% were of focal type and 37% of diffuse type.
4. 50% of the specimens had metaplastic epithelium. Among these 90% cases had pyloric metaplasia, 7% had intestinal and 3% had squamous metaplasia.
5. Dysplasia was present in 5.6% of cases, mostly mild type.
6. Carcinoma was detected in 0.44% cases.

## DISCUSSION

Whichever system is used for a particular purpose, it should be clinically useful and accurately reproducible, and with an acceptable level of inter-observer and intra-observer error. A simple and reproducible scoring system of chronic inflammatory cascade of gall bladder has been proposed in this study.

In all of the cases that we had subjected to this study, inflammatory mononuclear infiltrate was there and in majority it was a dense infiltrate. Lymphocytes were an intrinsic part of the chronic cholecystitis. The distribution of the infiltrate varies from focal to patchy to diffuse. Among other mononuclear cells apart from lymphocytes there were plasma cells and histiocytes. In about 20% of the cases of severe mononuclear cell infiltrate there was formation of lymphoid follicles. Follicular cholecystitis is used to describe this condition, in instances when the lymphoid hyperplasia infiltrates full thickness of the gall bladder wall[8,13]. Some studies show that mild or minimal mononuclear infiltrate represents an immunological barrier analogous to the barriers in other mucous membranes[14,15]. Epithelial hyperplasia was observed in 76% cases which also had a positive correlation with cases having severe form of chronic cholecystitis associated with erosions, fibrosis and severe mononuclear cell infiltrate. It has been observed that severe chronic cholecystitis is associated with acceleration of epithelial turn over[16]. Studies have confirmed cell proliferative activity in the background mucosa of gall bladder cancer[13,16]. Mucosal erosions that were associated with severe grade of activity in chronic cholecystitis showed a positive correlation with neutrophilic infiltrate and some correlation with cholelithiasis. It has been reported that lithiasis per se, or biochemical changes that contribute to its production, are an insult to the epithelium. Epithelial cells sloughing can liberate and add lipomucosomes to the biliary sludge and participate in gall stones formation[17]. With chronic cholecystitis, fatty degeneration of scattered epithelial cells appears to alter epithelial lining and favor metaplastic changes that could lead to other pathologic changes, including Ca in situ[13,16,18].

In chronic cholecystitis the mucosal folds may be flattened, ulcerated or normal. In our study 50% of cases showed epithelial metaplasia. Pyloric metaplasia was the commonest type followed by intestinal and squamous metaplasia. Our findings are in accordance with international studies showing pyloric metaplasia to be the commonest[19,20]. Metaplasia was associated mostly with cholelithiasis as has been reported elsewhere[16,20]. As there is acceleration of proliferative activity, in these areas the hyperplasia, progresses to higher grade i.e. metaplasia and Ca. in. situ[16,20,21]. This is supported by the fact that eighty percent of the invasive gall bladder Ca is associated with some degree of dysplasia in their vicinity[19,22]. In our study the presence of dysplasia is 5.6%, while in different studies it varies from 1-30%[12,16,19]. These dysplastic changes are mostly in the vicinity of other precursor lesions, initially involving the surface mucosa and gradually extending deeper into the glands[16,18,24]. Invasive adenocarcinoma was seen in 0.44% cases which are in accordance with the Ameet et al 0.78%, Bani- Hani et al 0.73% and Gurlayck G et al 1.0%[21,22,25]. Hyperplastic and metaplastic epithelium is more susceptible to malignant transformation in a sequence of dysplasia leading to carcinoma in situ and ultimately invasive carcinoma. All these changes are microscopic and cannot be deciphered on gross/ naked eye examination. In our study metaplasia was found in 50% of cases and hyperplasia in 76% of cases. Therefore one of the key aspects of this study is to stress upon identification of preneoplastic lesions in the gall bladder removed for presumed benign diseases, which justifies such an extensive microscopic study of customarily neglected surgical specimen. This is important because an early diagnosis of Ca has the best possible chance of treatment, which is limited to the wall of gall bladder.

## CONCLUSION

The nomenclature proposed is aimed to be clini-

cally useful and scientifically reproducible. The purpose of the study was to analyze inflammatory disease of gall bladder systemically with standard diagnostic terms and fixed criteria for making the final diagnosis. This checklist will significantly minimize the chances of missing any useful details in the biopsy specimens and will provide a rational and systematic diagnosis to the clinician so that they can have an accurate idea of the magnitude of the disease or its potential for simultaneous complications. Histopathological examination is therefore important in every cholecystectomy specimen.

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