

# Metaplasia-dysplasia-carcinoma sequence in cases of cholelithiasis: a histopathological study

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## Abstract

**Introduction:** Cholecystectomy is one of the most common abdominal surgeries performed across the world and in majority of the cases, is performed due to gall stones. The pathological changes related to gallstone formation are still the focus of intensive research. Presumably long standing gall stones produces a series of changes in the mucosa as a result of constant irritation, trauma and chronic inflammation. **Aim of the study:** The aim of our study was to find out the prevalence and sequence of metaplasia, dysplasia and malignancy in cholecystectomy cases due to gall stones. **Materials and methods:** A total 682 cholecystectomy specimen removed due to gall stones were studied for a two year period from April 2014 to March 2016. **Results:** Majority of the patients were females (75.22%). The youngest case was 15 years and oldest was 70 years of age. Antral metaplasia was noted in 41.05%, intestinal metaplasia in 4.5%, dysplasia in 2.34% and neoplasia 0.88% of cases. Histological continuity between epithelial changes was seen in 55 cases. 8 cases had continuity of antral metaplasia, intestinal metaplasia and dysplasia. 4 cases showed continuity of intestinal metaplasia with dysplasia and carcinoma and 3 cases showed continuity of dysplasia and carcinoma have a relationship. **Conclusion:** Hence it is inferred that metaplasia, dysplasia and carcinoma have an inter-relationship. Histopathological examination hence should be given utmost importance in all cases of cholelithiasis for identifying metaplasia, dysplasia and carcinoma.

**Key words:** Cholecystectomy, Intestinal metaplasia, Carcinoma Gallbladder

## Introduction

Gall bladder carcinoma is the sixth most common carcinoma of the digestive tract with an incidence of 2.5 cases per 100,000 in the United States [1]. There is a strong association between cholelithiasis and gall stones found in nearly 80% of cases [1]. A gall stone mainly injure the mucosal epithelium and thus causes changes like metaplasia, dysplasia and neoplasia. Mucosal dysplasia and carcinoma in situ are frequently found in mucosa close to invasive carcinoma. Current literature favors the hypothesis of epithelial metaplasia leading to dysplasia, carcinoma in situ and invasive cancer [2]. Presumably gall bladder containing stones develop cancer as a result of constant irritation, trauma and chronic inflammation. It has been observed that subcellular, biochemical, histochemical and molecular

alterations in epithelial cells of the gall bladder may precede the development of malignancy. Cholelithiasis is found in all cases of gall bladder carcinoma. Most of the gall bladder carcinoma originates in fundus (60%), body (30%) and neck (10%). Grossly 10-37% of gall bladder carcinoma cannot be identified with certainty.

Metaplasia usually progresses to dysplasia and adenocarcinoma via a multistep process which may result from accumulation of genetic changes. Cholelithiasis and even silent gall stones which are asymptomatic produce a series of epithelial pathological changes in gall bladder mucosa which could be precursor lesions of carcinoma. Therefore the study of dysplastic changes, other epithelial changes and malignancy associated with gallstone disease is important for better understanding of gall stone diseases.

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**Aim of the Study:** To find out the prevalence and sequence of metaplasia dysplasia and carcinoma of the gallbladder in cases of cholelithiasis.

**Inclusion Criteria:** All cholecystectomy cases done due to cholelithiasis.

**Exclusion Criteria:** All cholecystectomy cases done due to causes other than cholelithiasis; eg Cholesterosis cases, other cases of acalculous cholecystitis were excluded from the study.

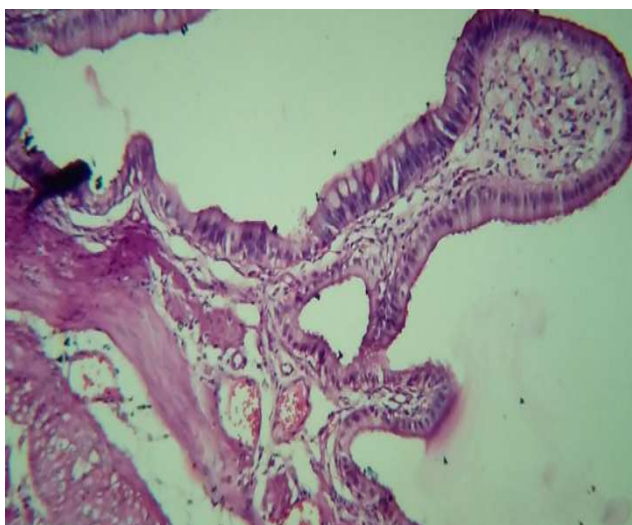
**Materials and Methods:** The study was carried out on 682 cholecystectomy specimens that were sent to the department of Pathology for histopathological examination. Detailed history, clinical findings,

investigations along with gross examination of gall bladder was done. The tissue was fixed in 10% formalin, processed routinely and embedded in paraffin. Three cross sections from each gall bladder were taken, one from the fundus, one from body and one from neck of the gall bladder. Further sections were taken in cases where possibility of an epithelial change was suspected. e.g. a hard area palpated while grossing was subjected to histopathological examination under microscope. Sections were stained with H & E. A detailed histopathological examination with respect to epithelial changes, metaplasia and neoplastic changes were carried out. Special stain (Periodic acid Schiff) was done in selected cases of gall bladder carcinoma to confirm the histological type.

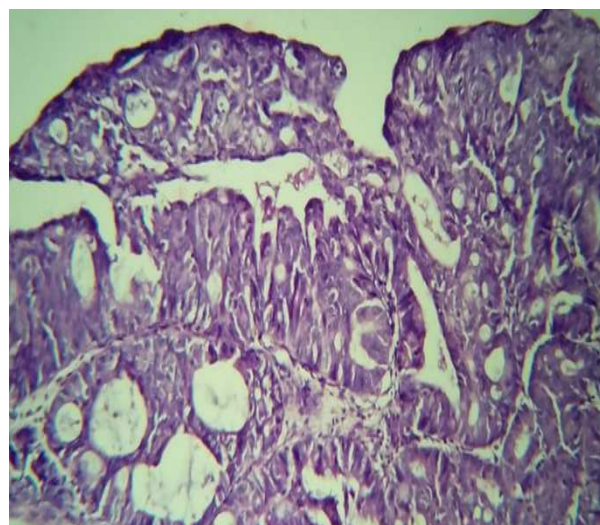
## Results

Majority of cases were females accounting for 75.22% cases. Female to male ratio was 3:1.53% of the cases were between 31-50 years of age. Age distribution of cases ranged from 15 years to 70 years. The mean age being about 42.3 years. Regarding Radiological investigations, Ultrasonography showed cholelithiasis in 98.83% of cases (674). Only 3 cases showed a definite gall bladder mass suggestive of carcinoma. Proliferation of mucous glands (Antral metaplasia) (Fig1a, b) was seen in 280 cases (41.05%). Antral metaplasia was identified as glands by cuboidal to columnar epithelium with large quantities of clear mucin having morphological resemblance to Brunner's glands. Intestinal metaplasia (Fig1) was seen in 31 cases (4.5%). Dysplasia was seen in 16 cases (2.34%), 2 cases (0.29%) showed features of carcinoma in situ (Fig2), while 6 cases (0.88%) showed features of malignancy (Fig3). Besides Xanthogranulomatous cholecystitis was noted in 26 cases (3.81%), Eosinophilic cholecystitis in 6 cases (0.88%).

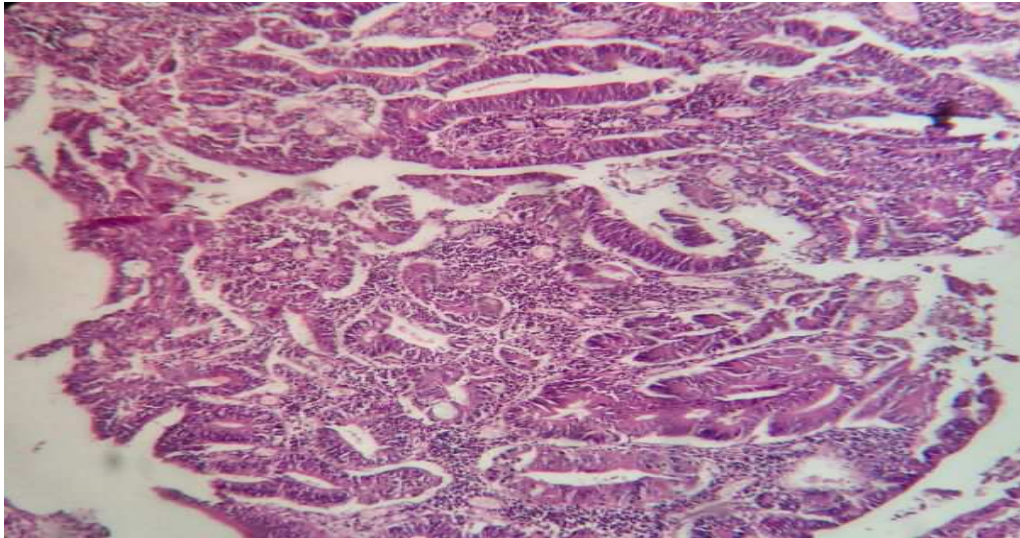
Out of 682 cases, antral metaplasia was present in 280 cases and intestinal metaplasia in 31 cases. In 26 cases both intestinal and antral metaplasia was present. Out of 31 cases of intestinal metaplasia 12 cases showed dysplasia. Histological continuity or blending was found between multiple epithelial changes in the same section in 35 cases. Of these 8 cases had continuity of antral metaplasia, intestinal metaplasia and dysplasia. 4 cases showed continuity of intestinal metaplasia with dysplasia and carcinoma and 3 cases showed continuity of dysplasia and carcinoma have an relationship.



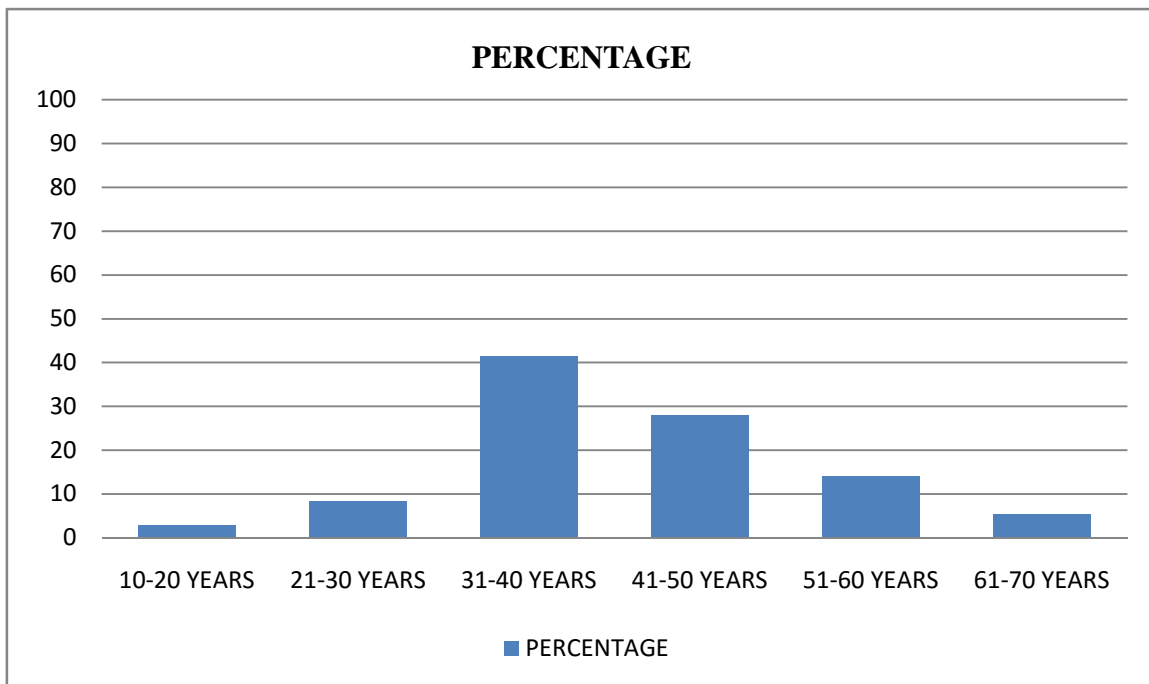
**Fig-1: Photomicrograph showing metaplasia  
10x10, H&E**



**Fig-2: Photomicrograph showing carcinoma in situ,  
H&E 10X10**



**Fig3: Photomicrograph showing adenocarcinoma of gall bladder, H&E 10X10**



Bar Diagram showing age wise distribution of cases

Diagnosis/lesion	Number	Percentage
Xanthogranulomatous Cholecystitis	26	3.81
Eosinophilic Cholecystitis	6	0.88
Metaplasia	311	45.6
Dysplasia	16	2.34
Carcinoma in Situ	2	0.29
Carcinoma	6	0.88

Chart showing disease distribution with percentage.

## Discussion

It is well known that gall stone is an important risk factor for the development of carcinoma gall bladder but causal relationship is still unproven. However the presence of gall stones in all the cases of carcinoma in our study suggest that there is a possible link. Martinez et al have also illustrated that low and high grade dysplasia, carcinoma in situ and invasive carcinoma were more frequent when cholelithiasis is present ( $p < 0.5$ ) than in cases without cholelithiasis [3].

The results of the study done by Vitteta et [4] al showed that primary carcinoma of gall bladder was also associated with single or multiple cholesterol gall stones that were impacting on the gall bladder wall. One important finding of our study was that all the cases of carcinoma had only cholesterol stones, pigmented stones were present in none of the cases.

The results of our study strongly suggest that cholelithiasis produces a series of mucosal pathological changes that represent the precursor lesions of carcinoma. The findings suggest that antral metaplasia and intestinal metaplasia are precursors of dysplasia in gall bladder. This is consistent with the findings of Mukhopadhyay S, et al, Mehta K.S. et al who suggested that dysplasia arises from a precursor lesion and not directly an inflammatory background [5].

In our study we observed that metaplastic changes were seen adjacent to dysplastic portions as well as in the areas of frank malignancy which further strengthens the hypothesis that dysplasia may occur in simultaneously metaplastic epithelium. 8 cases of our study showed a definite continuity of metaplasia, dysplasia and frank carcinoma. 3 cases showed continuity of dysplasia and frank carcinoma. Liatio M studied 71 cholecystectomy specimen and found dysplastic changes in 24 gall bladders [6]. Metaplasia was noted in 20 cases and in 14 cases was associated within the dysplastic portion. 3 out of 6 cases of our study showed dysplasia in direct continuity of carcinoma suggesting a definite close association between dysplasia and carcinoma.

The frequency of carcinoma in this study was 0.88% (6cases) which is consistent with the finding of gall bladder cancer reported by Gurlayck et al [7] as 1%, Mohan H et al [8] as 1.09% and Zahrani IH et al [9] as 1%. All the cases of our study were well differentiated adenocarcinomas.

Another important finding of our study is that the age difference of about 12 years is noted in the cases of dysplasia only and gall bladder carcinoma. It suggests that a period of 12 years is needed for dysplasia to convert into carcinoma. Roa et al have also studied preneoplastic lesions and gall bladder cancer [10].

They statistically analyzed the time required for change of dysplasia to carcinoma of gall bladder using age as main parameter and concluded that the period required to progress from dysplasia to carcinoma would be around 15 years observing a continuum in the progression of disease.

One thing from this study is clear that in the gall bladder epithelial changes cannot be recognized grossly or by radiological measures with certainty. Only 3 cases showed an ultrasonographic finding suggestive of carcinoma. Grossly not all cases of epithelial changes presented with a morphologically discernible change. The focal and patchy distribution of mucosal changes in gall bladder should be taken into account in studies designed to determine their actual incidence as limited number of histological samples usually taken in routine examination seem to be insufficient to detect all cases with dysplasia and /or carcinoma in situ, as may be inferred from randomly selected sections.

## Conclusion

It can be concluded that antral metaplasia, intestinal metaplasia, dysplasia and carcinoma have an inter-relationship. There is a significant higher incidence of carcinoma gall bladder in patients who harbor gall stone for longer period. Carcinoma of the gall bladder is notoriously lethal. Because early symptoms are vague and anatomically the gall bladder lacks a serosa to limit the spreading of cancer, the diagnosis of gall bladder cancer frequently occurs at an advanced stage, typically with an abysmal prognosis.

Histopathological examination is thus important in every case of cholecystectomy for identifying metaplasia, dysplasia and carcinoma. Even a prophylactic cholecystectomy can be advocated in patients harboring gall stones for a prolonged period to halt the neoplastic process.

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**Permission from IRB:** Yes

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