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Original Article

Histomorphological spectrum of gallbladder lesions- A prospective study from a teaching hospital

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Keywords:

Cholelithiasis;
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ABSTRACT

Background: Prevalence of gallbladder diseases vary with socio-demographic factors and in India it is around 2-29%. Cholelithiasis causes varied histopathological changes in gallbladder mucosa like acute and chronic inflammation, cholesterolosis, hyperplasia, metaplasia, dysplasia and carcinoma. Gallbladder carcinomas often present as an incidental finding in cholecystectomy specimens. Present study was conducted to identify spectrum of histopathological lesions and to find the incidence of gallbladder carcinoma in cholecystectomy specimens received at tertiary care centre in North Indian state of Uttarakhand.

Materials and Methods: A prospective study was conducted in the Department of Pathology, Government Medical College, Haldwani from January 2021 to September 2022. Total 760 cholecystectomy specimens were received during the study duration. Grossing of gallbladder specimens was done as per Gallbladder Carcinoma expert consensus statements.

Results: Out of 760 cholecystectomy specimens, 595 cases (78.29%) were obtained from females, with a female to male ratio of 3.6:1. Maximum cases were seen in 4th and 5th decades of life. Chronic cholecystitis was the most common histopathological diagnosis [709 cases (93.28%)], followed by acute cholecystitis in 20 (2.63%), follicular cholecystitis in 14 (1.84%) cases, 02 (0.26%) each of xanthogranulomatous cholecystitis and porcelain gallbladder, 05 cases (0.66%) of high-grade dysplasia and 08 cases (1.05%) of gallbladder adenocarcinoma. Out of 08 cases of gallbladder carcinoma, six were incidental diagnoses.

Conclusions: Histopathological evaluation of all resected cholecystectomy specimens is imperative for the detection of premalignant and malignant lesions that might escape in gross and radiological examination and thus could adversely affect patient outcome.

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INTRODUCTION

Gallstone disease is a major ailment suffered by modern society. There is a wide spectrum of disorders that afflict the gallbladder and this includes inflammatory, congenital, and neoplastic lesions. The signs and symptoms evoked by these underlying pathologies result in surgical intervention through the means of either open or laparoscopic cholecystectomy.[1] Prevalence of diseases of gallbladder vary with socio-demographic factors like age, sex, ethnic group and in India it is around 2-29%.[2] Cholelithiasis is believed to cause varied histopathological changes in gallbladder mucosa like acute

and chronic inflammation, cholesterolosis, hyperplasia, metaplasia, and dysplasia.[3] The most common types of gallbladder stones found are cholesterol and pigment stones. In North India, the incidence of symptomatic gallstones is 20 times higher than in South India, and nature of gallstones is mainly cholesterol/mixed type, whereas, pigment stones are more common in South India.[4] Prolonged stasis due to large gallstones leads to generation of reactive intermediates which can have a direct carcinogenic effect on gallbladder mucosa.[5]

Gallbladder carcinoma (GBC) is the most common biliary tract malignancy. It presents as diffuse thickening of the gallbladder wall, or as a mass lesion arising from fundus, body, or neck of the gallbladder.[6] India is a high incidence area for GBC and accounts for 10% of the global burden.[5] The North, East, North-East and Central parts of India have a much higher incidence rate for GBC when compared to South and West India.[7] Anatomopathological examination of cholecystectomy specimens in some cases reveal incidental gallbladder carcinoma (IGBC), which was not suspected before or during operation. In various studies the incidence of IGBC had been reported from 0.2% -2.1%.[8,9] Complete histopathological evaluation of all resected specimens is imperative for the detection of premalignant and malignant lesions that might escape in gross and radiological examination and thus could adversely affect patient outcome.

The present study was undertaken to study the spectrum of histopathological lesions in cholecystectomy specimens in a tertiary care hospital of Kumaon Region, so that we have a better understanding of gamut of gallbladder lesions in this belt of North India, and thus can aid the clinical team to streamline diagnostic and treatment modalities required for the management of gallbladder carcinoma.

MATERIALS AND METHODS

The present study was conducted at Department of Pathology, Government Medical College & Dr Susheela Tiwari Memorial Hospital, Haldwani, Uttarakhand, India from January 2021 to September 2022. Institutional ethical committee approval was taken for undertaking this study (Letter No. 619/GMC/IEC/2020/Reg. No. 579/IEC/R-06-01-2020). All open and laparoscopic cholecystectomy specimens received from Surgery department during this period were included in the study. Autopsy gallbladder specimens were excluded from the study. Demographic and clinical details of the patients were obtained from the patient's requisition form. All resected gallbladder specimens were received in 10% neutral buffered formalin. The gross features of the specimens were noted and in the initial sampling three random sections from gallbladder wall and cystic duct margin were submitted.[10] If polyp or tumor was identified grossly, then entire specimen was submitted. If on initial histopathological examination focal epithelial hyperplasia was seen, then additional two to four blocks were submitted and if high grade dysplasia or hyalinizing cholecystitis was seen then thorough sampling was done.[10] The sections were processed in automated tissue processor. Paraffin sections of 4–5-micron thickness was cut and stained by routine Hematoxylin and Eosin and examined under microscope. The data of total 760 cholecystectomy specimens, after excluding autopsy specimens was entered in a Microsoft excel sheet and analyzed using the statistical package of social sciences (SPSS) Version 28.0 software.

RESULTS

In the present study total 760 cholecystectomy specimens were received in the Department of Pathology, Government Medical College, Haldwani from January 2021 to September 2022. Out of total 760 cholecystectomy specimens, 595 cases (78.29%) were obtained from females, and 165 cases (21.71%) from males, with a female to male ratio of 3.6:1. Maximum cases were seen in 4th and 5th decades of life. The mean age of patients was 43.13±14.03 years. There was significant preponderance of female patients in each age group (Table-1).

Table 1: Age and gender wise distribution of cases

Age Group (Years	Female	Male	Number(%)
<20	15	3	18 (2)
20-30	137	20	157 (21)
31-40	144	44	188 (25)
41-50	130	42	172 (23)
51-60	107	29	136 (18)
>60	62	27	89 (12)
TOTAL	**595**	**165**	**760 (100)**

In this study calculi were retrieved in 348 cases. Mixed cholesterol (234 cases, n=67.24%) and pure cholesterol (70 cases, n=20.11%) stones were more common, and seen in 304 cases (87.36%), while pigment stones were observed in 44 cases (12.64%) (fig.1)

Chronic cholecystitis was the most common histopathological diagnosis in this study and was observed in 709 cases (93.28%), followed by acute cholecystitis in 20 cases (2.63%), follicular cholecystitis in 14 cases (1.84%), 02 cases (0.26%) each of xanthogranulomatous cholecystitis and porcelain gallbladder, 05 cases (0.66%) of high-grade dysplasia, and 08 cases (1.05%) of gallbladder adenocarcinoma (fig.2)

Total 709 cases of chronic cholecystitis had a plethora of associated histopathological findings amongst which pyloric metaplasia was the commonest and seen in 292 cases (41.18%), followed by cholesterolosis in 179 cases (25.24%). Other associated findings were low grade dysplasia in 54 cases (7.62%), focal xanthogranulomatous reaction in 41 cases (5.78%), spongioid hyperplasia in 25 cases (3.53%) adenomyomatous hyperplasia in 09 cases (1.27%), intestinal metaplasia in 08 cases (1.13%) and 01 case (0.14%) of osseous metaplasia. 100 cases (14.10%) of

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chronic cholecystitis had no associated findings (fig.3).

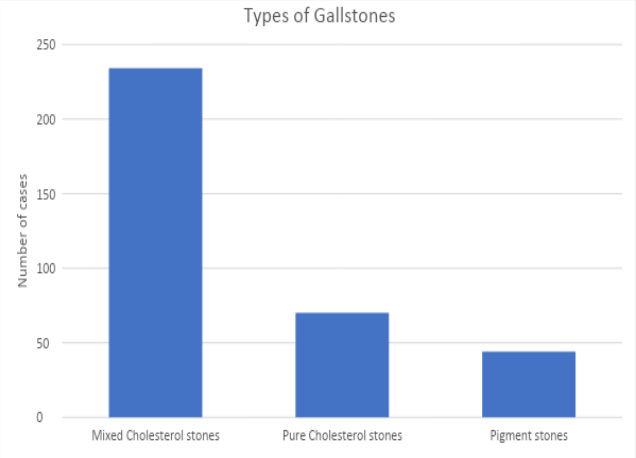

Figure 1: *Bar diagram showing gallstones based on morphology*

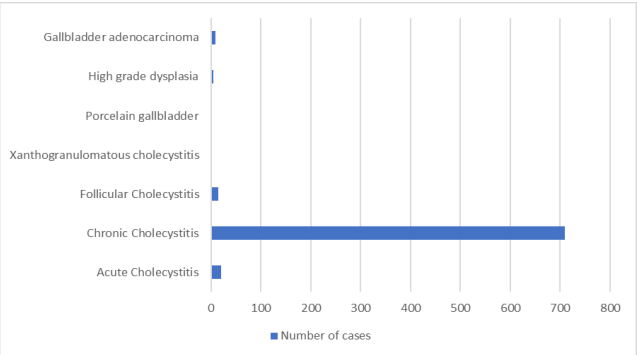

Figure 2: *Bar diagram showing histopathological diagnosis of cholecystectomy specimens*

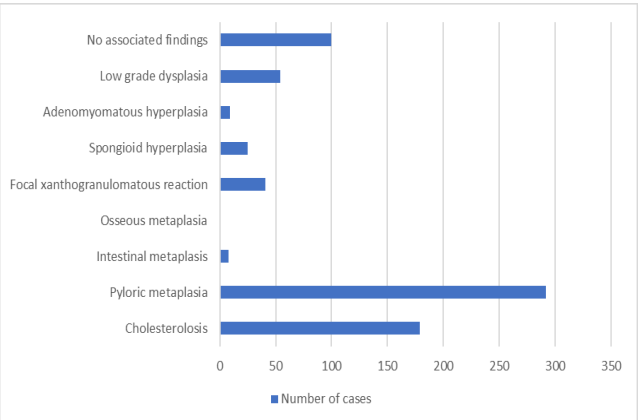

Figure 3: *Bar diagram showing histopathological lesions associated with chronic cholecystitis*

DISCUSSION

Gallbladder diseases are on a rise in the recent times due to the sedentary lifestyle, calorie rich diet, and increasing prevalence of obesity. Gallbladder specimens are one of the most frequently encountered specimens in most histopathology laboratory. Though they comprise a major bulk of routine histopathology, yet they remain vastly underexamined due to selective sampling in most laboratories.

The most common ailment involving the gallbladder is cholelithiasis followed by cholecystitis. Cholelithiasis is a chronic hepatobiliary disease that is characterized by the formation of gallstones in the gallbladder, common bile duct and hepatic bile duct.[11] Gallstone causes various pathological changes in gallbladder mucosa such as acute and chronic inflammation, cholesterolosis, hyperplasia and carcinoma.[12] Gallbladder carcinoma is the most feared diagnosis as it is often detected in advanced stage due to non-specificity of symptoms, which culminates into a poor clinical outcome.

In the present study out of total 760 cases, 595 cases were obtained from the females, with a female to male ratio of 3.6:1, which was comparable to study by Almas T et al and Mushtaq M et al.[13,14] Increased estrogen levels in females increase cholesterol excretion in the bile leading to its supersaturation, and hence a 2-3 times higher risk of gallstones in reproductive aged females as compared to their male counterparts. In pregnancy gallbladder evacuation function also suffers which further increase the risk of gallstone diseases, especially in multiparous females.[15]

In the present study, the age of the patients ranged from 12 years to 78 years and average age of presentation was 43.13 years, whereas for malignant lesions it was 53 years. Maximum cases who underwent cholecystectomy for gallbladder diseases were seen in 4th and 5th decades of life (Table1), which was similar to study by Almas T et al [13] and Beena D et al.[16]

In the present study calculi were retrieved in only 348 cholecystectomy specimens out of the total 760 cases examined. In these 348 cases, mixed cholesterol/pure cholesterol stones were more common and seen in 87.36% of cases, whereas pigment stones were seen in 12.64% of cases (fig.1&3). Jayanthi V et al had observed in their study that gallbladder bile in control group of healthy liver donors and in cholelithiasis patients from North India had significantly higher cholesterol concentration as compared to their counterparts from South India.[4] This finding explains the high prevalence of mixed/cholesterol stones in North India. In the remaining 412 cases, gallstones had been reported in the imaging studies but were removed intraoperatively by the surgeons.

Chronic cholecystitis with associated pyloric metaplasia and cholesterolosis (fig.2&3)was the most common pathology observed in our study. This was similar to study by Kotasthane VD et al, Beena D et al, and Almas T et al.[13,16,17] Chronic cholecystitis histologically presents as chronic inflammatory cell infiltrate, gallbladder wall thickening and mucosal changes such as metaplasia which could sometimes culminates into dysplasia and malignancy.

Other uncommon findings associated with cholecystitis were 14 cases (1.84%) of follicular cholecystitis (fig.5), 01 case (0.13%) of osseous metaplasia (fig.6), and 02 cases (0.26%) of porcelain gallbladder (fig.7). Osseous metaplasia in the

benign gallbladder is a very rare finding. This condition was first described by Huggins and Sammet and till date only few cases of heterotopic ossification in the gallbladder wall had been reported.[18,19] Heterotopic ossification may occur as an isolated finding or in association with dystrophic calcification. Chronic injury associated with cholecystitis and cholelithiasis is the inciting factor for both heterotopic ossification and dystrophic calcification.[19]

Cholesterolosis results from accumulation of cholesterol esters and triglycerides in gallbladder mucosa. It is presents as an incidental finding in abdominal sonography or is diagnosed on histopathological examination of cholecystectomy specimens. It is a noninflammatory condition which is usually asymptomatic and had no malignant potential.[20,21] In our study, cholesterolosis was seen in 23.55% of the cases (fig.8) while in the study by Almas T et al it was observed in 32.80% of the cases. Whereas, in the study conducted by Mondal B et al and Beena D et al it was observed in 2.92% and 2.50% of the cases respectively.[3,13,16] The exact cause of high prevalence of cholesterolosis in north indian population as compared to South and East India is not known but dietary differences between these regions might be responsible.

Xanthogranulomatous cholecystitis (XGC) is characterized by the presence of foamy histiocytes, fibrosis, and chronic active inflammation in the gallbladder wall and is usually associated with gallstones. The clinical and radiological findings in XGC can mimic GBC and its association with GBC is well established.[22] Diffuse XGC was observed in 0.26% of the cases in our study and is associated with increased wall thickness (fig.9) whereas focal xanthogranulomatous reaction was seen in 5.39% of cases. In a study by Almas T et al and Mondal B et al, it was observed in 1.13% and 1.65% of the cases, respectively.[3,13]

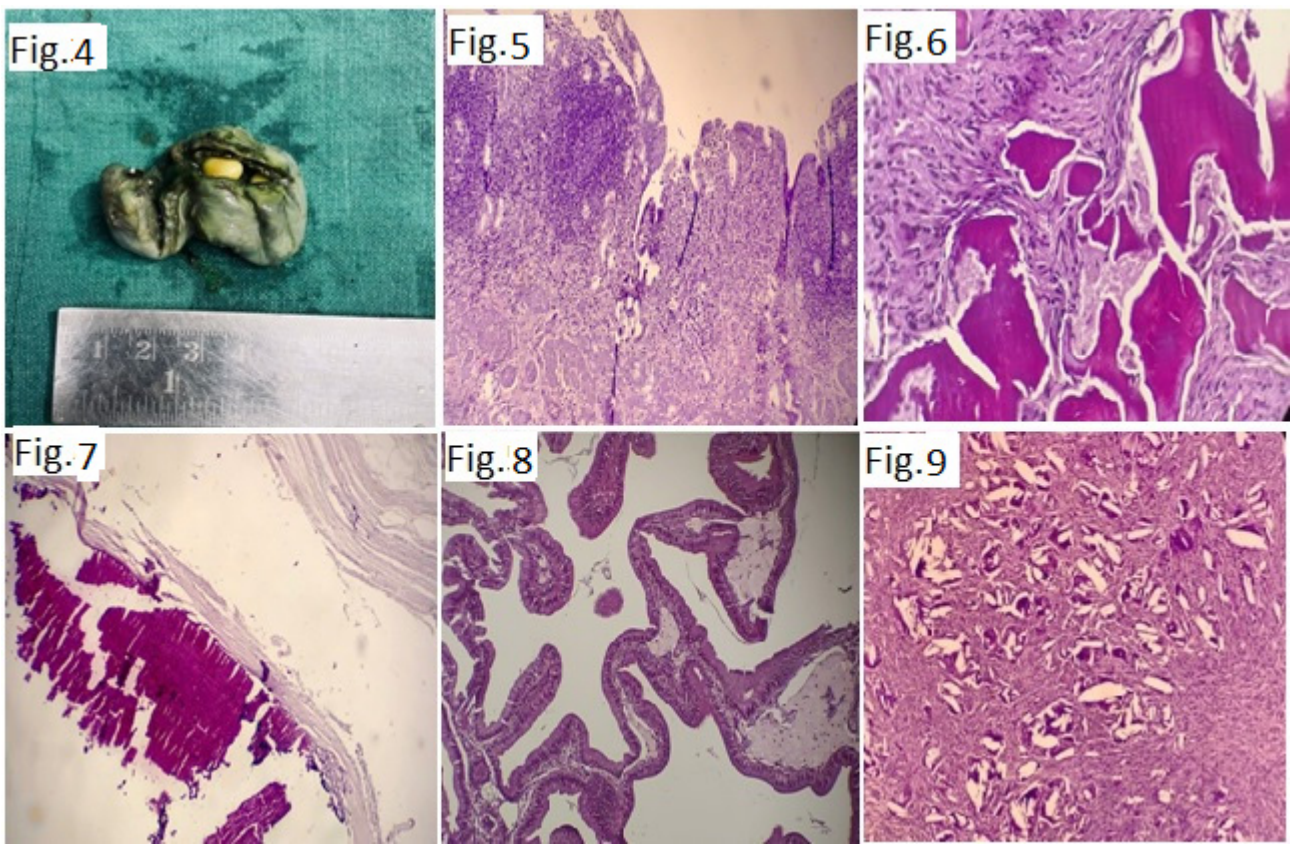

Figure 4-9: *[fig. 4] –Partial cut open gallbladder with cholesterol stones; [fig. 5]-Follicular cholecystitis Photomicrograph shows lymphoid follicles with germinal centre in gallbladder mucosa (HE; X100); [fig. 6]-Photomicrograph shows heterotopic calcification in gallbladder wall (HE; X100); [fig. 7]-Porcelain gallbladder-Photomicrograph shows diffuse dystrophic calcification of gallbladder wall (HE; X100); [fig. 8] – Cholesterolosis - shows collection of foamy macrophages in lamina propria. (HE; X100); [fig. 9]- Xanthogranulomatous cholecystitis- Photomicrograph shows fibrosis and cholesterol clefts surrounded by multinucleated giant cells and histiocytes.(HE; X100)*

In our study metaplasia and dysplasia were observed in 39.47% and 7.76% of the cases, respectively (fig. 10-12). Mondal B et al had found metaplasia in 4.70% of the cases, and dysplasia in 2.16% of the cases.[3] Whereas, Mukhopadhyaya et al had reported metaplasia in 69.25% of the cases and dysplasia in 5.0% of the cases.[23] This variance in the incidence of metaplasia between different studies could be due to geographic and ethnic differences, or may be due to variations in the number of sections examined in grossly normal cholecystectomy specimens. Albores-Saavedra

J et al had stated that detection of focal epithelial change is affected by the number of sections examined.[24] Thus, it was observed that detection of metaplasia and dysplasia was higher with extensive or whole gallbladder mapping, as compared with single random histologic sections.[23] As cited by Mukhopadhyay et al, various studies from Japan had found similarities in the histochemical profiles of pyloric metaplasia, intestinal metaplasia, and carcinoma, further attesting to the hypothesis that GBC is derived from metaplastic epithelium.[23,25,26] The incidence of intestinal and antral type metaplasia showed a close association with the presence of gallstones and inflammation. The sequential steps in the development of carcinogenesis could be stated as: Gallstones----Chronic Inflammation----Antral type metaplasia----Intestinal metaplasia----Dysplasia----Carcinoma.[23]

GBC contributes to 85-95% of biliary tract malignancies worldwide.[27,28] The incidence of GBC is higher in developing nations.[29] Females are affected 2 to 6 times more commonly than males.[30] The main risk factors for GBC are gallstone disease, porcelain gallbladder, gallbladder polyps, primary sclerosing cholangitis, chronic salmonella infection, *Helicobacter Pylori* infection, congenital biliary cyst with pancreatico-biliary malformation, exposure to carcinogens and obesity.[27] Most of the GBC are diagnosed late due to non-specificity of the symptoms.[31] In symptomatic patients, pain is the most common complaint followed by anorexia, nausea, vomiting, and jaundice.[27] In advanced GBC overall mean survival is 6 months, while 5-year survival is only 5%. An inverse correlation exists between cholecystectomy for cholelithiasis and GBC rate in endemic areas. Though prophylactic cholecystectomy is not advised for clinically silent gallstones, but it provides hope for secondary prevention in endemic areas and in patients with additional risk factors such as very large stones (≥ 3cm) or elderly female with cholelithiasis.[32]

In the present study 8 (1.05%) cases of GBC were diagnosed out of the total 760 cases examined (fig. 13,14) Different studies have reported incidence rates for GBC ranging from 0.2% to 2.33%.[13,17] Out of these 8 cases, 6 (0.79%) cases were incidentally diagnosed on routine histopathological examination and were not associated with specific imaging findings.(fig.15) Jha V et al had rendered the diagnosis of incidental gallbladder carcinoma (IGBC) in 0.41% of cases. Shi SP et al had observed in their study that pre-operative imaging had failed to diagnose 50% of GBC.[8,9] Certain authors had suggested that IGBC are mostly early stage (pT1a, pT1b) and therefore, simple cholecystectomy is the management of choice.[33,34] Though in our study all cases of IGBC were pT2a or pT2b (fig.14), and required radical cholecystectomy to improve patient outcome.[8] Hence, it is concluded that histopathological examination of all resected cholecystectomy specimens is required to detect and pathologically stage IGBC which in turn culminates into a better clinical outcome as compared to GBC.

Table 2: Clinico-pathological profile of cases of gallbladder carcinoma

S.No.	Age/ Sex	Clinical diagnosis	Radiological findings (USG)	Histological diagnosis & Pathological stage
1.	65y/M	Chronic cholecystitis with cholelithiasis.	Chronic cholecystitis with intraluminal gallbladder mass [size=26x19mm], Multiple stones of size 2 to 2.2mm are seen	Moderately differentiated adenocarcinoma [pT2aNxMx]
2.	35y/F	Chronic calculous cholecystitis.		Moderately differentiated adenocarcinoma [pT2aNxMx]
3.	60y/F	Chronic calculous cholecystitis with choledocholithiasis.	Two small calculi (5.7mm and 4.0mm) are seen in lumen of gallbladder. Common bile duct is dilated (11.3 mm), a large calculus is seen in lumen of common hepatic duct and common bile duct	Moderately differentiated adenocarcinoma [pT2bNxMx]
4.	65y/F	Chronic cholecystitis with cholelithiasis.	20-25mm calculi seen in gallbladder lumen	Well-differentiated adenocarcinoma [pT2bNxMx]
5.	65y/F	Chronic cholecystitis with cholelithiasis.	Chronic calculous cholecystitis with choledocholithiasis	Moderately differentiated Adenocarcinoma [pT2aNxMx]
6.	42y/F	Chronic cholecystitis with cholelithiasis.	Mass gallbladder neck	Well differentiated adenocarcinoma [pT2bNxMx]
7.	40y/M	Chronic cholecystitis with cholelithiasis.	Cholecystitis with thick bile and cholelithiasis	Moderately differentiated adenocarcinoma [pT2aN0Mx]
8.	52y/F	Chronic cholecystitis with cholelithiasis.	Multiple calculi in gallbladder lumen of size (8-12.5mm)	Poorly cohesive (Signet ring cell) carcinoma [pT2bNxMx]

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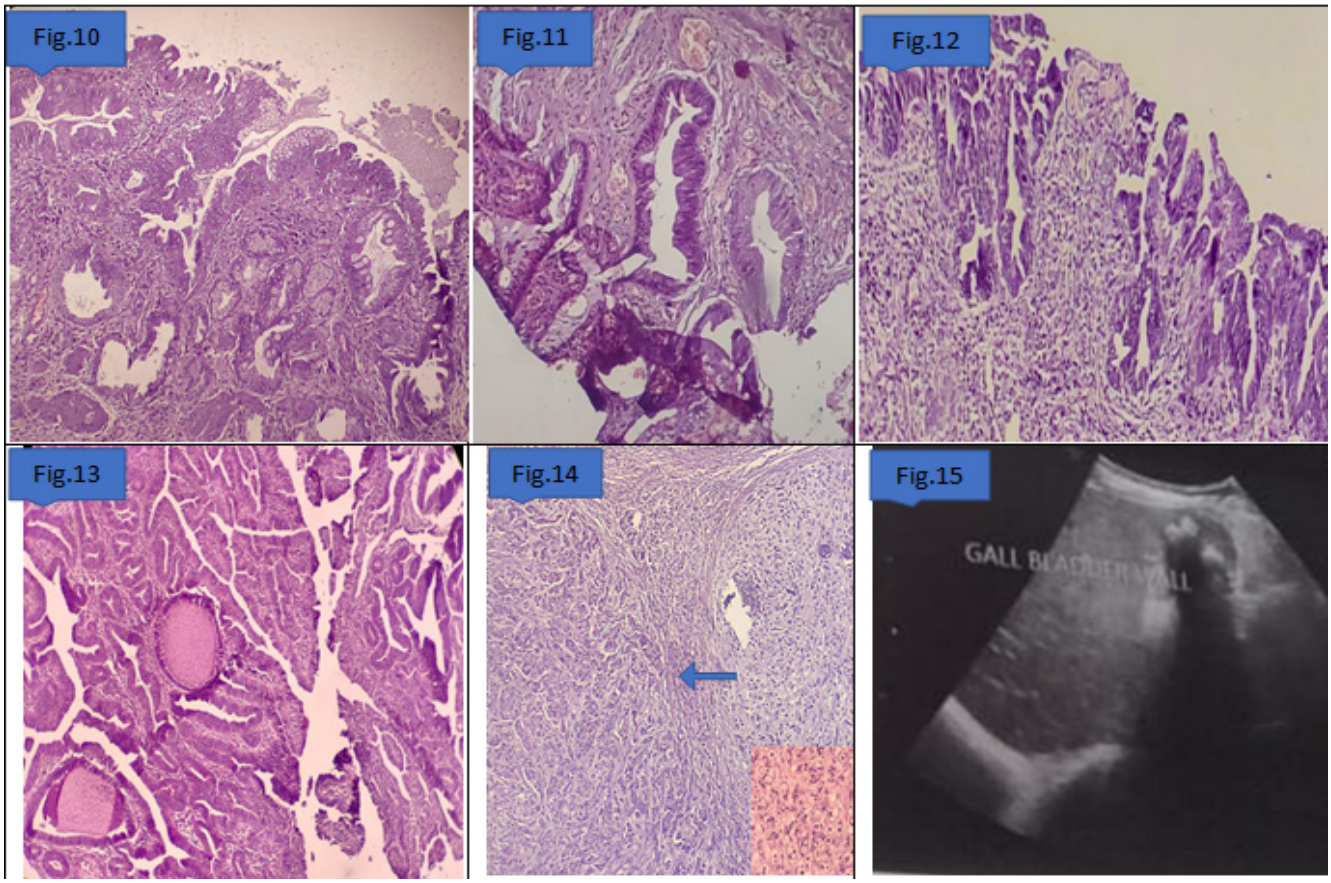

Figure 10-15: *(fig. 10)-Gallbladder mucosa showing patchy intestinal and pyloric metaplasia (HE; X100). (fig. 11)- Photomicrograph shows features of low-grade dysplasia with abrupt transition from adjacent normal mucosa (HE; X100); (fig. 12)- High-grade dysplasia with extensive mucosal involvement and no surface maturation (HE; X100); (fig. 13]-Photomicrograph shows well differentiated gallbladder adenocarcinoma with intraluminal necrosis (HE; X100) (fig. 14):-Poorly cohesive gallbladder adenocarcinoma reaching upto hepatic bed {arrow pointing towards hepatic bed} (HE; X100). Inset showing signet-ring morphology of tumor cells (H&E;400X); (fig. 15)-Ultrasound Gallbladder of the same case as in fig. 11. Shows diffusely thickened gallbladder wall (7mm) with contracted lumen and multiple calculi (average size 8.1-12.5 mm)*

CONCLUSIONS

The present study highlights the broad spectrum of gallbladder lesions which were encountered during our study duration. There was female preponderance in our study, which was comparable to other studies from North India. Chronic cholecystitis was the most frequently encountered pathological entity in this study, which was comparable to other studies. Mixed/cholesterol gallstones were more common than pigment stones in this study, which was similar to other studies from North India. Pyloric metaplasia was the most common lesion associated with chronic cholecystitis, followed by cholesterolosis. Out of eight cases of gallbladder adenocarcinoma in this study, six were incidental diagnoses with non-specific pre-operative imaging findings, emphasizing the fact that gallbladder though may appear simple yet it exhibits diverse spectrum of pathologies.

Although selective sampling of cholecystectomy specimens can be cost-effective in a resource limited setting, it could lead to falsely negative diagnosis of early-stage carcinoma with normal imaging and gross findings, and hence increased risk of mortality, if timely curative treatment is not offered. Therefore, careful histopathological examination of all gallbladder specimens is strongly recommended especially in high-risk regions like North India.

Limitation of the study

In this study stones had been retrieved in only 348 cases (45.79%), therefore an exhaustive study between type and number of calculi and associated mucosal changes could not be performed in all the cases.

Conflicts of Interest: None

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