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A retrospective histopathological analysis with clinicoradiological correlation of gallbladder diseases in a tertiary care centre in Bihar- A retrospective study.

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Abstract

Background: Diseases of the gall bladder are a common health issue affecting the population worldwide. The spectrum of the disease ranges from inflammatory lesions to dysplasia and further extends to carcinomas. Histopathological examination is the gold standard diagnostic modality. The diagnostic process is amplified when histopathological findings are correlated with clinicoradiological features.
Aims and objectives: The study aims to highlight the histopathological spectrum of gall bladder lesions and it's clinicoradiological correlation, thereby advancing the understanding of gall bladder pathology and its management.

Materials and methods: A retrospective observational study was conducted in the Pathology department at IGIMS, Patna. Cases were selected as per the inclusion and exclusion criteria from 3100 cholecystectomy samples received from January 2021 to December 2024. Details were collected from histopathology request forms and hospital records. Gross and microscopic features were analysed, and the parameters were calculated.

Results: The mean age of the patient was 42minus 4.76 years, with the majority in the age group of 41 to 50 years, having a female predominance. A significant association was observed between increased gall bladder wall thickness and adenocarcinoma. Cholecystectomy performed in patients less than 10 years of age had a direct relationship with choledochal cyst. Radiological and histopathological diagnosis corroborated in 89% percent of cases.

Conclusion: Most gall bladder lesions have an inflammatory origin, with a female preponderance. Cholecystectomy is the treatment of choice. Increasing incidence of malignancy emphasizes the importance of thorough histopathological examination in confirming the preoperative diagnosis and simultaneously sampling any suspicious areas to rule out an incidental finding of malignancy.

Recommendations: Routine histopathological examination of all cholecystectomy specimens is recommended to detect incidental malignancies. Prospective studies and improved radiological protocols are needed to enhance diagnostic accuracy and patient outcomes.

Keywords: *Cholecystitis, Cholesterolosis, Cholelithiasis, Adenocarcinoma, Dysplasia, Gall bladder*
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Introduction

Gall bladder pathologies are one of the most frequently encountered diseases occurring globally, with the lesions ranging from non-neoplastic conditions like congenital anomalies, cholelithiasis, cholesterolosis, cholecystitis, hyperplasia, and metaplasia to premalignant conditions and carcinomas [1]. The symptoms and signs elicited by these pathologies require the need for surgical intervention in the form of cholecystectomy, either laparoscopic or open. Chronic cholecystitis is the most common pathology of the gall bladder, occurring worldwide as well as in India, and is associated with cholelithiasis in about 80% - 90% of the cases [2,3]. Chronic cholecystitis associated with cholelithiasis irritates the mucosal lining, heralding the onset of metaplastic and dysplastic changes, predisposing the patient to the development of carcinomas [4,5]. In India, cholelithiasis is seven times more common in the northern region, with the highest prevalence in the states of Bihar, Uttar Pradesh, West Bengal, Orissa, and Assam, owing to the differences in the diet, lifestyle, and environmental conditions [6,7]. Sedentary lifestyle, obesity, fatty diet, alcohol intake, gallstones, insulin resistance, high triglyceride level, pregnancy, and certain drugs are risk factors for the development of gall bladder diseases. Clinically, the patient may remain asymptomatic or may complain of vague abdominal pain, discomfort, and flatulence.

Gall bladder cancers (GBCs) account for 0.5% - 1.09% of all gall bladder lesions. These are either clinically suspected, radiologically diagnosed, or at times incidentally diagnosed following cholecystectomy or cholelithiasis [1]. Chile reported the highest incidence of GBCs, with the incidence among females of 27.3 cases per 100000 person years [7]. India is a high-incidence area for GBCs. In India, GBCs exhibit regional disparities. The studies on cancer data from northern India showed GBCs accounting for 9.6% of all cancers in females, becoming the third leading site for cancer in females. However, studies from eastern India showed GBCs to comprise 5.8% - 6% of all cancers [8]. The incidence of GBCs in India has been steadily increasing, especially in Bihar, as per the National Cancer Registry Programme (ICMR–NCDIR, 2020). 40% - 90% cases of GBCs are associated with cholelithiasis [9]. In patients with a long history of cholecystitis, a suspicion of malignancy warrants thorough histopathological workup [10]. Incidental GBCs are found in approximately 0.5% - 1.1% of all cholecystectomies [11]. Ultrasonography is a valuable initial radiological investigation of choice. However, advanced imaging modalities like CT, MRI, endoscopic ultrasonography, and magnetic resonance cholangiopancreatography are increasingly being employed for differential diagnosis and to assess tumour extent. Complete laboratory workup, including complete blood count, liver function test, lipid profile, and random blood sugar estimation, helps distinguish the aetiology of the gall bladder diseases and further helps in identifying the associated complications [12]. The accurate diagnosis of gall bladder diseases rests on the histopathological examination, which guides the treatment decisions and prognosis. A multimodality approach utilizing both traditional and modern diagnostic procedures will improve the patient survival rate.

The study aims to highlight the various histopathological changes in cholecystectomy specimens and emphasize the importance of histopathological analysis along with its clinical and radiological correlation in the diagnostic evaluation of gall bladder diseases.

Methodology

Study design

A retrospective, observational study

Study setting

The study was conducted at the Department of Pathology in Indira Gandhi Institute of Medical Sciences (IGIMS), Patna, Bihar, India.

Study population and time of study

A total of 3100 cholecystectomy samples from January 2021 to December 2024 were selected as per the following inclusion and exclusion criteria.

Inclusion criteria

Formalin-fixed cholecystectomy specimens resected for clinically diagnosed gall bladder diseases and received in the Pathology department.

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Exclusion criteria

Small biopsies of the gall bladder, Cholecystectomies associated with other surgeries, eg, Whipple's resection
Autolysed and poorly preserved specimens

Data collection and study procedure

After selecting the cases as per the inclusion and exclusion criteria, all the details were collected from the histopathology request forms and hospital record sheets. Gross and microscopic features were recorded and analysed.

Statistical analysis

Data analyses were done using SPSS version 23. Quantitative variables were expressed as mean±SD, whereas qualitative variables were expressed as absolute and relative frequencies. Chi-square test and z test were used as tests of significance. A p-value of less than 0.05 was considered significant.

Ethical clearance

The study protocol was reviewed and approved by the Institutional Ethics Committee, Indira Gandhi Institute of Medical Sciences, Patna, Bihar, India.

Informed Consent

Written informed consent was obtained from all participants before their enrolment in the study.

Results

A total of 3100 cholecystectomy specimens received during the study period in our department were analysed on the basis of clinical, surgical, radiological, and histopathological parameters. Out of 3,100 cases, laparoscopic cholecystectomy was performed in 2,635 (85%) cases, with the remaining 465 (15%) undergoing open laparotomy (Fig. 1).

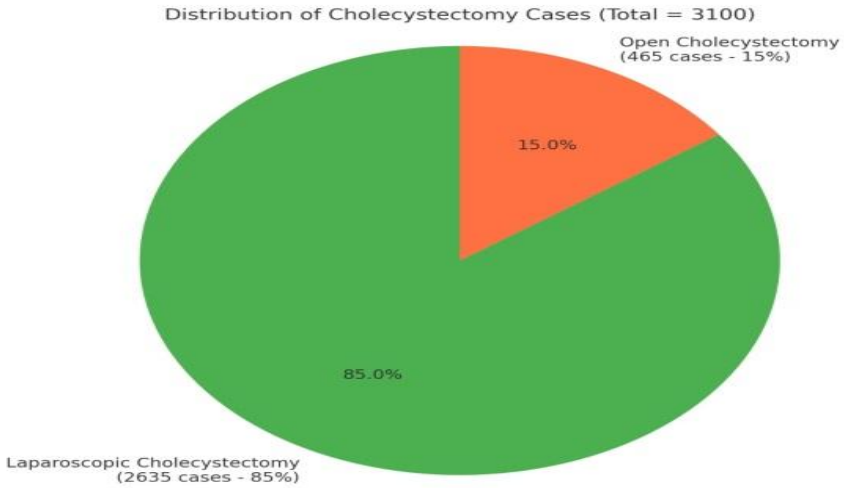

Figure 1. Distribution of cases undergoing laparoscopic and open cholecystectomies

Our patients ranged in age from 3 years to 81 years, with a mean age of 42minus 4.76 years. In cases of non-neoplastic lesions, the patient's age ranged from 3 years to 81 years, with a mean age of 41.81±14.71 years. The youngest patient having a malignant lesion was 27 years, with the

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oldest being 73 years, giving a mean age of 51.81±11.85 years (Table 1).

Table 1. Comparison of benign, pre-malignant, and malignant lesions

Characteristic	Benign Lesions	Pre-Malignant Lesions	Malignant Lesions
Age (Mean plusminus D)	41.81±14.71	40.46±14.02	51.81±11.85
Gender (M/F)	646/2007	39/99	96/213
No. of cases	2653 (85.58%)	138 (4.45%)	309 (9.97%)

Data were presented as either mean±SD or n (%)

57 cases of cholecystectomy were performed in less under 10 years of age, and 25 cases were associated with choledochal cyst (43.9%). 5 cases of choledochal cyst were noted in the age group of 11 to 20 years, 3 cases in the range of 31 to 40 years, 1 case in the 41 to 50 years age group, and 2 cases in the age group of 51 to 60 years. Hence, in patients less than 10 years of age, choledochal cyst was the indication for cholecystectomy. Overall, females were more commonly afflicted by the diseases of the gall bladder, giving the female to male ratio of 3:1 (Fig. 2). Female to male ratios in non-neoplastic and neoplastic lesions, respectively, were 3:1 and 2.2:1.

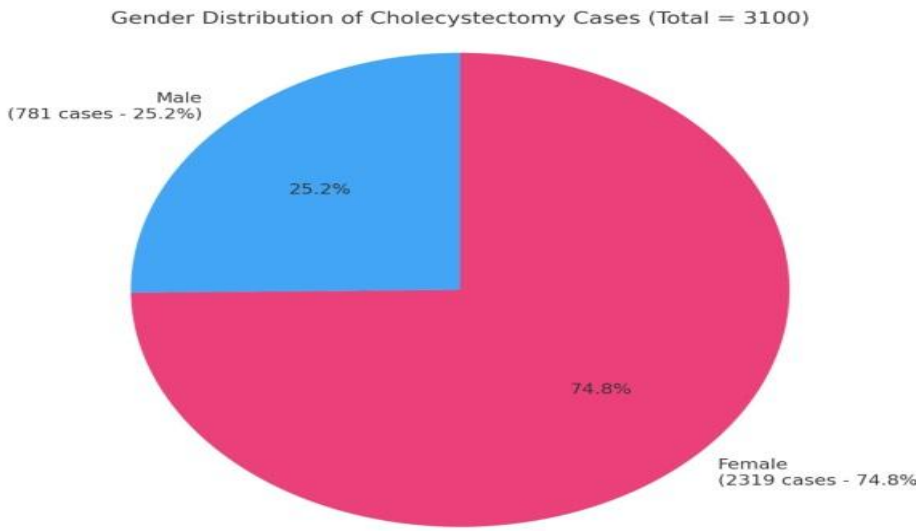

Figure 2. Gender wise distribution of cases

Histopathology revealed chronic cholecystitis as the commonest gall bladder disease (2349 cases, 75.8%). 138 cases (4.5%) showed premalignant lesions comprising of cholecystitis with low grade dysplasia (7/138 cases, 5%), chronic cholecystitis with high grade dysplasia (12/138 cases, 8.7%), intracholecystic papillary neoplasm (2/138 cases, 1.5%), porcelain gall bladder (1/138 cases, 0.7%), pyloric metaplasia (98/138 cases, 71%) and intestinal metaplasia (18/138 cases, 13%). 309 cases (10%) were observed to be malignant lesions, out of which 305 (98.7%)

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were adenocarcinoma of the gall bladder, and the remaining 4 cases (1.3%) were identified as moderately differentiated squamous cell carcinoma. 45 cases of adenocarcinoma were well differentiated (14.6%), 226 cases (73.1%) were moderately differentiated, and 34 cases (11%) were poorly differentiated adenocarcinoma. The histopathological diagnosis with the demographic details is provided in Table 2.

Table 2. Demographic details with histopathological diagnosis

Histopathological Diagnosis	N (%)	Age (Meminus D)	Gender(M/F)
Acute Cholecystitis	124 (4)	45.34±8.33	31/93
Chronic Cholecystitis	562 (18.1)	37.27±15.75	138/424
Follicular Cholecystitis	15 (0.5)	46.77±13.99	3/12
Cholelithiasis	1586 (51.1)	40.98±14.12	387/1199
Choledochal Cyst	36 (1.2)	12.93±14.74	10/26
Cholesterolosis	165 (5.3)	43.31±13.94	39/126
Mucocele/Pyocele	11 (0.4)	45.45±12.72	3/98
Xanthogranulomatous Cholecystitis	124 (4)	46.77±12.71	28/96
Hyperplasia(Adenomyomatous/Papillary/Spongiform)	30 (0.9)	35.45±15.67	7/23
Intracholecystic Papillary Neoplasm	2 (0.1)	40.5±5.0	1/1
Metaplasia(squamous/pyeloric/intestinal)	117 (3.8)	96±**15.81**	34/83
Dysplasia(low grade/high grade)	19 (0.6)	41.74±**12.50**	4/15
Carcinoma(Adenocarcinoma/Squamous cell carcinoma)	309 (10)	54.85±12.15	96/213
Total	3100 (100)	-	781/2319

Data were presented as either mean±SD or n (%)

Cholelithiasis was present in 1586 cases of non-neoplastic lesions (60%) and 174 cases of neoplastic lesions (56%) (Table 3).

Table 3. Correlation of cholelithiasis with benign and malignant lesions

Characteristic	Pre-malignant and Malignant lesions	Benign Lesions	p-value
Chronic Cholecystitis with Cholelithiasis	174 (253.78) [25.08]	1586(1506.22) [4.23]	Chi-square statistics is 67.7982, p-value is <0.00001
Chronic Cholecystitis	273 (193.22) [32.94]	1067 (1146.78) [5.55]	
Total	447	2653	Significant at p-value<0.05

Premalignant lesions were predominantly found in females (40 cases) and in the age group of 31 to 40 years. Females also showed a higher prevalence of carcinomas (213cases). The age group most commonly affected was more than 60 years (Table 4)

Table 4. Correlation of gender with the distribution of carcinoma cases

	Carcinoma		Total	p-value
Gender	Yes	No		Chi-square statistic is 6.2844, p-value is 0.012181
Female	213 (231.15) [1.43]	2106 (2087.85) [0.16]	2319	
Male	96 (77.85) [4.23]	685 (703.15) [0.47]	781	
Total	309	2791	3100	Significant at $p < 0.05$

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Most common clinical presentation was abdominal pain which occurred in 2387 cases (77%), followed by flatulence (1302 cases, 42%), nausea and vomiting (1085 cases, 35%), jaundice (651 cases, 21%) and backache (527 cases, 17%) (Table5).

Table 5. Clinical presentation of gallbladder diseases

Symptoms	No. of cases	Percentage (%)
Pain abdomen	2387	77
Flatulence	1302	42
Nausea/Vomiting	1085	35
Jaundice	651	21
Backache	527	17

Out of 3100 patients, 620 cases (20%) showed a random blood sugar level of more than 150mg/dl. Increased blood sugar level proved to be a significant risk factor for the development of gall bladder diseases, with an odds ratio of 2.49. Leucocyte count of more than 12000 cells per microliter of blood was noted in 1767 cases (57%). Increased serum cholesterol levels were identified in 133 cases (4.3%). Increased serum bilirubin levels were seen in 158 cases (5.1%).

Ultrasonography successfully diagnosed 2759 cases (89%) of gall bladder diseases. However, 341 cases were not accurately diagnosed. 189 cases (55.4%) of chronic cholecystitis with wall thickness of more than 5mm and 43 cases (12.6%) of cholelithiasis were diagnosed as malignant neoplasm. Other lesions which were misdiagnosed as gall bladder carcinomas comprised 97 cases (28.5%) of xanthogranulomatous cholecystitis, 9 cases (2.6%) of adenomyomatous hyperplasia, 2 cases (0.6%) of intracholecystic papillary neoplasm, and a single case (0.3%) of porcelain gall bladder. Figure 3 shows an H&E-stained intracholecystic papillary neoplasm (40X). Figure 4 shows H&E-stained adenocarcinoma of the gall bladder, which is moderately differentiated (40X). Figure 5 shows H&E-stained follicular cholecystitis (40X). Figure 6 depicts H&E-stained chronic cholecystitis with cholesterolosis and pyloric metaplasia (40X).

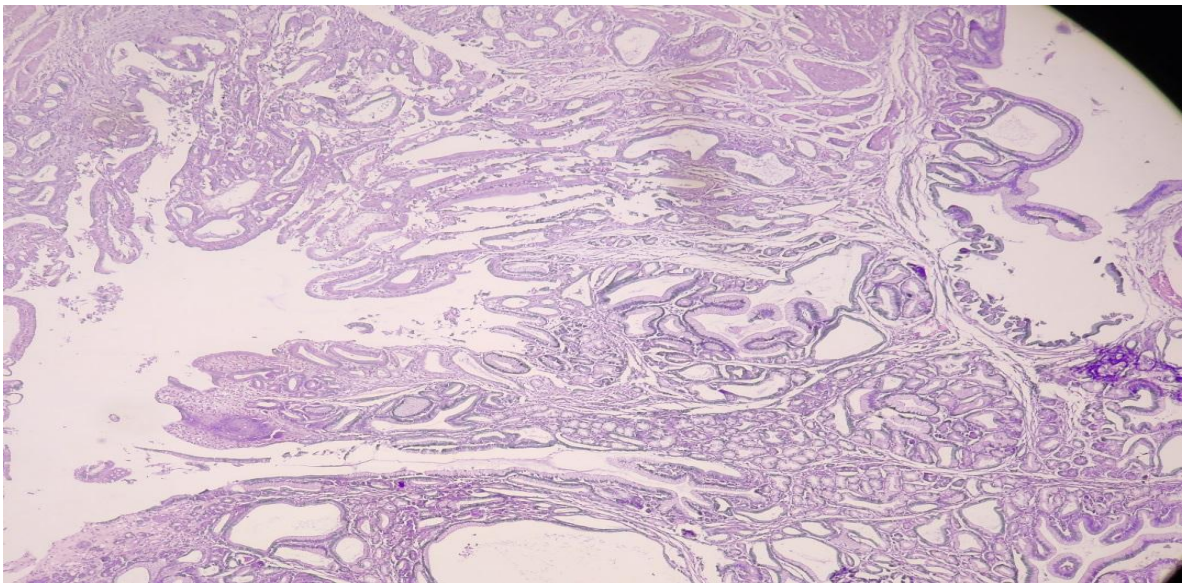

Figure 3. H&E (40X) Intracholecystic papillary neoplasm

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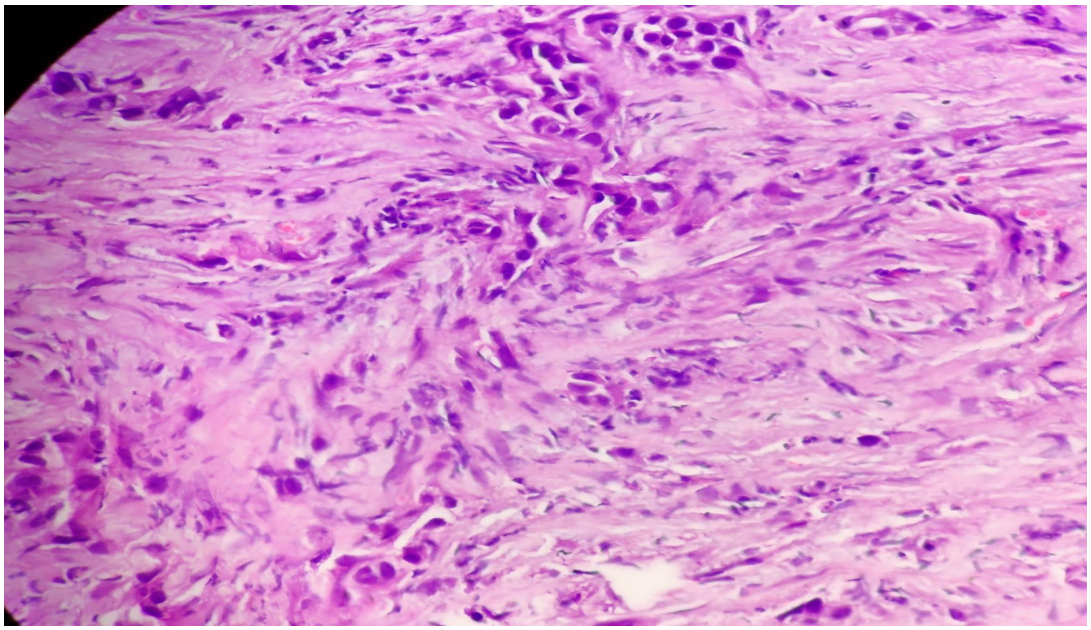

Figure 4. H&E (40X) Adenocarcinoma of the gall bladder – moderately differentiated

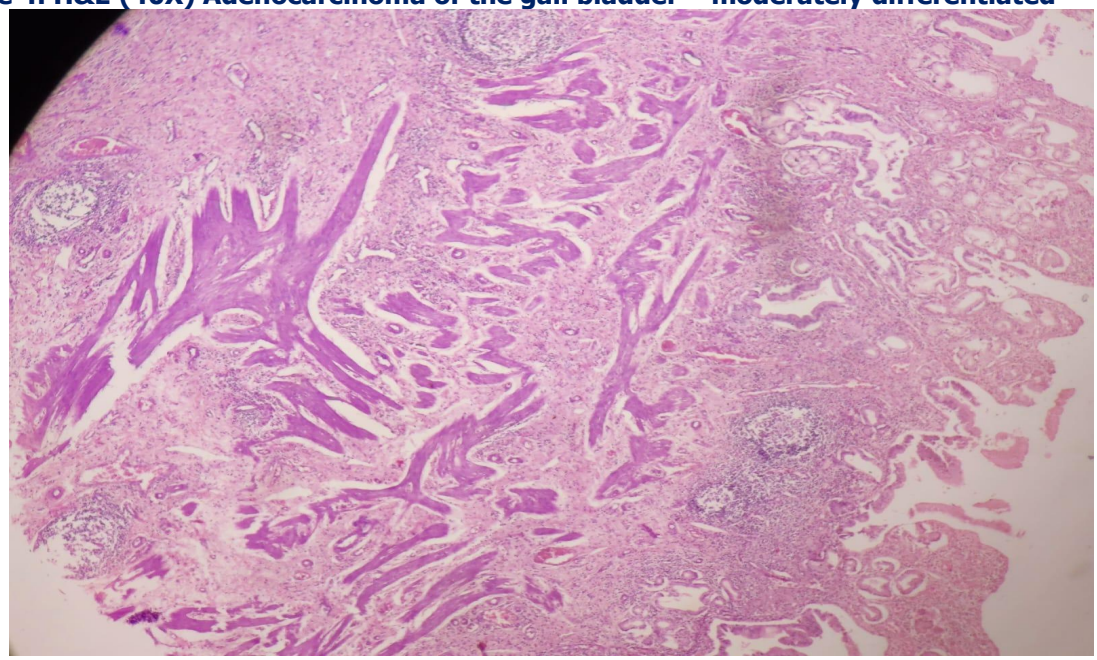

Figure 5. H&E (40X) follicular cholecystitis

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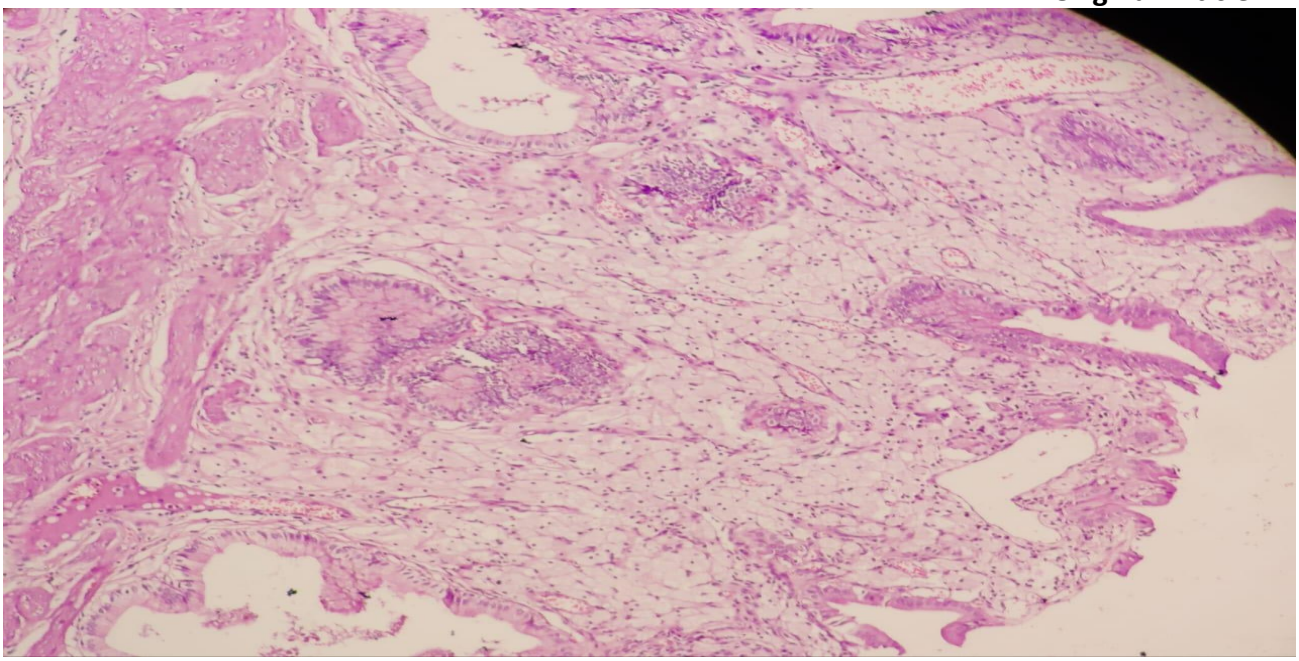

Figure 6. H&E (40X) chronic cholecystitis with cholesterolosis and pyloric metaplasia

Discussion

Cholecystectomies are a commonly performed procedure for gall bladder diseases, which shows a significant worldwide variation in distribution [7]. In our study, the mean age for neoplastic and non-neoplastic lesions was 51.81±11.84 years and 41.81±14.71 years, respectively, with the non-neoplastic lesions occurring in a younger age and the neoplastic lesions presenting relatively at an advanced age. The mean age for premalignant neoplastic lesions was 4.46±14.02 years. Studies done by Dowerah et al also highlighted the same findings [13]. Both the non-neoplastic and neoplastic lesions showed a female preponderance with a female-to-male ratio of 3:1 and 2.2:1, respectively. The overall female-to-male ratio in our study was 3:1.Selvi TR et al in their study concluded that gall bladder diseases were predominantly seen in females (61.5%) as compared to males (38.4%) [14]. Several other studies conducted by Mondal B et al [15], Dattal DS et al [16], Agrawal R et al [17], and Almas T et al [18] showed concordance with our studies regarding gender distribution and age of presentation. Few studies have reported a higher distribution ratio amongst females [19,20,21]. Hence, it can rightly be said that gall bladder diseases are common in females, attributable to the role of female sex hormones and sedentary lifestyles as the risk factors. In our study, 43.9% of cholecystectomies performed in patients less than 10 years of age were associated with choledochal cyst, making it the most common indication for cholecystectomies in the paediatric age group. The findings are consistent with the studies done by Kevin C Soares et al [22].

In this study, it was seen that 1760 cases of gall bladder diseases were associated with cholelithiasis. 1586 cases of non-neoplastic and 174 cases of neoplastic lesions showed the presence of gallstones, respectively. Chi-square test showed a statistic value of 67.7982 with a p-value of <0.00001 (Table 3). These findings are consistent with the findings of other studies done by Srivastav AC et al [7], Ahrendt SA et al [23], and Agarwal S et al [24]. The study also showed a significant correlation between the female gender and carcinoma of the gall bladder with chi chi-square statistic value of 6.2844 and a p-value of 0.012181 (Table 4). This is by the study of Gupta V et al [25]. In our study, the non-neoplastic lesions outnumbered the neoplastic lesions, giving similar results as inferred by the studies of Srivastav AC et al [7].

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Abdominal pain and the accompanying symptoms of nausea and vomiting were the most frequent clinical presentations of patients. Similar findings have been reported by other studies as well [26,27,28,29,30].

Carcinomas comprised 10% of the cases in our study, with 1.3% cases diagnosed as squamous cell carcinoma. Studies done by Yadav A et al [31] and Siddiqui FG et al [28] showed 4.7% and 2.7% of their cases as malignant, respectively. The Gangetic belt, particularly in the states of Bihar and Uttar Pradesh, is known for having a high incidence of gall bladder carcinomas compared to other regions of India [32].

341 cases in this study, which were diagnosed as malignant lesions radiologically during preoperative routine examination, were confirmed as benign lesions on histopathological examination. These cases comprised xanthogranulomatous cholecystitis (97 cases), cholecystitis with wall thickness of more than 5mm (189 cases), calculous cholecystitis (43 cases), adenomyomatous hyperplasia (9 cases), intracholecystic papillary neoplasm (2 cases), and porcelain gall bladder (single case). This study showed an association of 89% between the ultrasound imaging and histopathological diagnosis. Studies done by Ostapenko et al stated that there exists a discrepancy between preoperative ultrasound findings and final histopathology results [33].

Conclusion

This study reinforces the importance of diligent examination of all operated cases of gall bladder specimens with thorough sampling of all thickened areas and with representative sectioning of suspicious areas for an accurate diagnosis. Frozen section is an effective diagnostic modality to differentiate true invasive carcinomas from clinical and radiological mimickers. A multidisciplinary approach integrating clinical, radiological, intraoperative, and histopathological findings will ensure adequate diagnosis.

Limitations

As this study is retrospective, there is a limitation on the patient follow-up, which would have further highlighted the disease-free survival rates in premalignant and malignant lesions. Prospective studies highlighting the role of early diagnosis, especially in premalignant conditions, will be helpful.

Recommendations

Routine histopathological examination of all cholecystectomy specimens is recommended to detect incidental malignancies. Prospective studies and improved radiological protocols are needed to enhance diagnostic accuracy and patient outcomes.

Generalizability

The study's findings are generalizable primarily to populations in eastern India, particularly regions like Bihar with similar dietary habits, environmental exposures, and gallbladder disease prevalence. However, being a single-centre, retrospective study, its results may not fully apply to other regions or healthcare settings.

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Source of funding

The study was self-funded by the department, with no external funding.

Conflict of interest

The authors declare no conflict of interest.

Author contributions

All authors contributed to the study design, data collection, analysis, and manuscript preparation.

Data availability

The data generated during this study are available from the corresponding author upon reasonable request.

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