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Histo-Pathological Evaluation of Gall bladder Diseases at Jorhat Medical College and Hospital, (One Year Retrospective Study)

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Abstract: ***Gallbladder (GB) diseases, is one of the most frequent findings in surgical OPD as well as emergency care in Government hospitals. Most of cases usually presenting with pain in the right upper abdomen, sometimes associated with a palpable mass mostly irregular size and shape. Pain as described by the patients is shooting in nature. And often requires surgical intervention and post of histopathological examination. Material and Method: we started collecting cases in our histopathology department in last one year retrospective. Out of 884 no.of total cases, 413 was gallbladder with a 46.7% of the total. Cases were sending to Pathology, and request for histo-pathological examination of the same. Observation and Results: Total no specimen was collected in 884 out no of males 121against 292 of females. "Acute on Chronic cholecytis with cholelithiasis was seen 52.1% which is a very usual finding and co-relate with the national studies. Discussion: Various types of gall bladder masses were operated for in different surgical setting and went on histo-pathological examination. The estimated prevalence of cholelithiasis in India has been reported between 2% and 29%. Present study co-relate with national data.***

Keywords: Gallbladder disease, cholelithisis, cholecystitis, gallbladder carcinoma etc.

1. Aim of Study

To find out incidence of different histopathology of gallbladder in Jorhat Medical College and Hospital including different age groups, sex ration including socio-economic and food habits in this area.

2. Introduction

Gallbladder disease is as common as the human race. Medical history witnessed many cases of upper abdominal pain associated with fever and vomiting, nausea, retching, belching etc. and most of the time "There was palpable lump" in the right upper part the abdomen.

It has been observed in Egyptian mummies dating as far back as 3400 B.C. It appears likely that Charaka (two centuries B.C.) and Sushruta (six centuries B.C.) from India were also familiar with this disease of the biliary tract. [1]

Most commonly seen in females having 2-3 child births, around 4th decade, usual on high fat diet associated with obesity. Sometimes it present with acute abdomen that requires immediate resuscitation and hospitalization with significantly good outcome.

Cholelithiasis produces diverse histopathological changes in gallbladder mucosa, namely acute inflammation, chronic inflammation, granulomatous inflammation, hyperplasia, cholesterolosis, dysplasia, and carcinoma.[2,3] When a patient with cholelithiasis becomes symptomatic, therapeutic intervention is necessary

Out of all Gallbladder (GB) diseases, cancer gallbladder (GBC) is one of the most frequent findings in Government hospital. It is one of the most prevalent and lethal cancer of hepato-biliary tract expressing its multifocal etiologies and represents distinct ethnic, gender and geographical variations at the time of diagnosis

3. Review of Literature

Gall Bladder as Mass (Benign) as on the upper abdomen:

GB Mass as Cholelithiasis

Cholelithiasis, or gallstones, represents the most commonly encountered gallbladder

Mass. They affect over 25 million individuals or about 10% of the U.S. adult population, affecting women more than men by a ratio of 2:1; the risk increases with age.

Common associations include diabetes, oral contraceptives, estrogen replacement, obesity, ileal disease, total parenteral nutrition, cirrhosis, and certain medications. Gallstones are seen about 95% of cases as acute cholecystitis, nearly 65% of adenomas, 95% of porcelain gallbladders, and 90% of gallbladder adenocarcinomas.

About 80% of stones are cholesterol stones (contain greater than 50% cholesterol; 10% being pure cholesterol), and the remaining 15-20% are pigmented stones (contain <25% cholesterol), which are primarily composed of calcium bilirubinate and glycoproteins.

Common Investigation (USG or Ultra sonography):

Ultrasound is the most common type of investigation employed for initial evaluation of the gallbladder. Ultra Sonography is highly sensitive and specific for cholelithiasis, detecting >95% for stones over 2mm. Gallstones are classically mobile and strongly echogenic with marked posterior acoustic shadowing.

CT sensitivity for detection of gallstones is much less than sonography, typically about 75%-80% for stones ≥5mm. Calcium containing stones are well seen, even as small as 2mm; however, pure cholesterol stones may be iso- or even hypoattenuating to bile, decreasing detection rates.

MR detection of gallstones is best appreciated on T2-weighted images, especially magnetic resonance cholangiopancreatography (MRCP) sequences.

Benign mass (Gallbladder) Polyps:
Gallbladder polyp is another very clinical condition in most of the surgical OPD patients. Polyps are varying pathological, sizes and types as described by the textbooks. Sometimes it represents as a single epithelial adenomatous polyp and sometimes as a pedunculated, serrated of varying sizes containing different physio-chemical constituents as per different biochemical conditions.

Gallbladder polyps represent a spectrum of processes presenting with similar morphology and appearance at imaging.

Cholesterol polyps comprise about 50% of gallbladder polyps, are typically less than 10mm in size, and are completely benign with no malignant potential.

Adenomatous polyps of the gallbladder represent true neoplasms, representing about 5% of polyps seen in polyposis syndromes, such as Peutz-Jeghers and familial adenomatous polyposis. Subtypes of adenomas include tubular, papillary, and tubulopapillary. Most lesions measure less than 20mm in size and 10% are multiple.

Computerized Tomography (CT):
CT, adenomatous polyps are typically iso- or hypodense to liver parenchyma and are more easily seen than cholesterol polyps.

The MR appearance of polyps is nonspecific with polyps having intermediate signal intensity on T1 and T2 weighted images. The appearance overlaps with gallbladder carcinoma.

Irie et al. reported that malignant polypoidal lesions are more often have increased signal on diffusion images with lower ADC values than benign polyps at high b-values.

Other benign mass like Adenoma and Adenomyomatosis:
On the basis of the growth pattern, adenomas can be tubular, papillary, or tubulopapillary.

The tubular type is the most common and consists of small compact glands separated by fibrous stroma.

Cytologically, adenomas are classified as pyloric, intestinal, foveolar, and biliary. Tubular adenomas of the pyloric type are the most common and may be associated with foci of squamoid Spindle cell metaplasia

Adenoma arising from muscular hyperplasia is known as adenomyomatous hyperplasia or diverticular disease of the gallbladder represents one of two acquired benign hyperplastic cholecystoses.

The most important features of adenomyomatosis are intraluminal cholesterol deposition that becomes trapped within dilated Rokitansky-Aschoff sinuses, along with bile salts, sludge, and calculi.

Ching et al reported 36 cases of either adenomyomatosis or gallbladder carcinoma and demonstrated a sensitivity of only 36% for the 22 pathologically proven cases of adenomyomatosis with a negative predictive value of only 44-48%.

CT cannot be used to effectively exclude adenomyomatosis, if well-defined cystic gallbladder wall thickening is encountered in the absence of other suspicious findings, it is reasonable to conclude the diagnosis of adenomyomatosis.

MR imaging is the “Pearl necklace” sign, which results from the dilated Rokitansky-Aschoff sinuses in adenomyosis.

A study compared 47 patients with either adenomyomatosis or primary gallbladder carcinoma using single shot fast spin echo T2-weighted magnetic resonance cholangiopancreatography sequences. It was demonstrated that the “Pearl necklace” sign could be used to diagnose adenomyomatosis and exclude carcinoma with a mean sensitivity, specificity, and accuracy of 62 %, 92%, and 74%, respectively.

Yoshimitsu et al. described that both adenomyomatosis and primary carcinoma enhance from the arterial phase through the delayed phase, but there were differences in their enhancement distribution.

In another study, Haradome et al., reported that contrast enhanced MR demonstrated that enhancement patterns were indistinguishable between adenomyomatosis and carcinomas in 70% of their patients.

Gall bladder Metaplasia
Metaplastic epithelium in the gallbladder consists of two major types: gastric and intestinal. Both tend to occur in the setting of chronic cholecystitis, as well as in association with dysplasia or adenocarcinoma.
Gastric metaplasia recapitulates the gastric pyloric or antral mucosa. Focal gastric metaplasia is seen in around 50% of gallbladders with chronic inflammation.

Metaplasia and Dysplasia:
The overall pathogenesis of adenocarcinoma is thought to result in evolution from dysplasia (atypical hyperplasia) to carcinoma or from adenoma to carcinoma. Metaplastic changes may or may not be premalignant, but a high incidence of associated metaplasia exists in gallbladders with adenocarcinoma, especially in those carcinomas with intestinal differentiation.

Common Gallbladder Sludge
Gall bladder sludge is very clinically important sometimes mimic as mass. Biliary stasis from prolonged fasting or

hyperalimentation is some possible reason to explain to some extent.

Sludge presents as a layering slowly, dependent fluid-fluid level, tumefactive sludge presents as an intraluminal polypoid, echogenic, non-shadowing mass, which may mimic a tumor.

Biliary Intraepithelial Neoplasia

Clinical Features
Precursor lesions of adenocarcinoma are now grouped under the term BilIN and include dysplasia and CIS. These lesions are classified into low (BilIN-1), intermediate (BilIN-2), and high grade (BilIN-3), as in the bile 13.5% and BilIN-3 in 1.6% to 3.5% of resected gallbladders and in as many as 40% to 88% of the gallbladders with adenocarcinoma.

The average age at time of diagnosis for invasive carcinoma was in the mid-50s.

In another study, the mean age for patients with precursor lesions averaged 69 years, with a similar time span expected for the development of invasive adenocarcinoma. On the basis of these data, the period for evolution from BilIN to invasive adenocarcinoma would be around 15 years. These studies also suggest that BilIN may occur at an earlier age in some populations, and women are affected more often than men.

Other important clinical malignant tumor or mass:

Primary Gallbladder Carcinoma
Primary carcinoma of the gallbladder ranks as the fifth most common malignancy of the gastrointestinal tract. Adenocarcinoma accounts for 75% to 85% of cases. This is a disease of old age, with a peak incidence occurring at 70 to 79 years of age and a female-to-male predominance of 3 : 1.

Microscopic Features

The most common neoplasmis adenocarcinoma, with the following recognized histologic subtypes: **biliary, intestinal, gastric foveolar, mucinous, signet ring cell, clear cell, cribriform, adenosquamous, squamous, hepatoid, carcinosarcoma, and undifferentiated**. Biliary type is the most common, which may be well (>95% glands), moderately (50%-95% glands), or poorly differentiated (<50% glands). In well differentiated tumors, the glands are lined by columnar to cuboidal tumor cells resembling those of normal gallbladder. The tumor cells are arranged in sheets, cords, or glands or in a cribriform pattern. The nuclei are usually round to oval and are often located basally or centrally. The cytoplasm may be eosinophilic, slightly granular, pale, clear, or mucinous.

Gallbladder carcinoma is very difficult and almost impossible using sonography in grading and staging.

Bach et al. reported that only 37% of patients with advanced disease could be identified on US. In another study, Tsuchiya described that 30% of early carcinomas may be missed by ultrasound.

Early gallbladder imaging features of carcinoma have significantly overlapped with those of benign gallbladder diseases. There are several features, however, that may be useful in characterizing a mass as suspicious for malignancy.

Malignant mass or polypoid lesions are typically greater than 1 cm. Also, any focal or diffuse wall thickening >1 cm or asymmetric thickening are suggestive of carcinoma.

Gallstones and porcelain gallbladder are well described risk factors, although the association between gallbladder carcinoma and porcelain gallbladder may not be as evident as previously thought.

Kahn et al. of seven published series encompassing over 60,000 cholecystectomies found gallbladder carcinoma in 15% of porcelain gallbladders; gallbladder carcinoma in itself had an overall incidence of 0.2%. They also retrospectively reviewed an additional 1,200 consecutive cholecystectomies with 1.1% having porcelain gallbladders, as well as an additional series of 35 gallbladder carcinomas.

4. Material and Method

The study was carried out in the Deptt.of Pathology, Jorhat Medical College and Hsopital,Jorhat, Assam for a period of one year from Jan2020 to Dec 2020. Total no specimen was collected in 884 out no of males 121against 292 of females. Out of which there was few specimen which was said to be younger age group and few other samples received which was marked “Senior citizen”.

Total No. of Cases in Histo-pathology deptt: 884

Total No. of GB specimen was 413.

Methodology

(The classical histo-chemical method) was used. Tissue specimen sends from Indoor Surgical Deptt.of General Surgery, JMCH to the histopathology deptt. Requesting for biopsy. Tissue usually fixed in 10% formalin as per protocol to the deptt.

Once, the tissue is received in the deptt. the fixatives used to change as per tissue histo-technique as described by Culling’s el al. sometimes it is necessary change with the second fixative in next 24 hrs depending upon the condition of tissue fixation/condition.

Different tissue fixatives are used for different tissues as described by histo-techiniques bu Culling et al.

After careful examination, when confirmed, tissue is allowed to go on the process of dehydration by ascending graded of alcohol followed by cleaning and impregnation as the process described by surgical anatomy by Rosai and Ackermann. Than it is followed by embedding, which is done by standard process, followed by paraffin block (melting 54° C and tissue is cut into 3-5 µm/diameter by

rotary microtome and placed in an pre-coated albumin slides. If necessary cut the ribbon with the warm blade of a knife followed by staining.

Section staining is done by hematoxyline and eosin as a routine method. (H&E, Harris Hematoxylin, powdered hematoxylin in ahcohol along with ammon.alum, ethyl alcohol and $Hgcl_2$ and water is mixed as per the process described by Culling et al.
Preliminary treatment of the slide is done by as by standard method followed by counter staining with 1% aqueous solution of eosin for a minute. Than it passes through ascending grades of alcohol and finally absolute alcohol, followed by dehydration by alcohol, clear in xylol and mounted in Canada balsam etc.

Results: A well stained preparation should shows Nuclei-blue, acidophilic nuclei- Red, Basophilic nuclei-Blue, Muscle, Collagen and Fibrils-Pink, Red cell-Pink, Eosinophilic granules-Red, Basophilic granules-Blue, in general cytoplasm-Blue. Special care is taken when bony tissue and fatty tissue was received. Uses of various histo-chemical staining is used for different tissues as per guide line as described by Culling et al.

Some of photograph while doing grossing in our institute:

5. Observation and Results

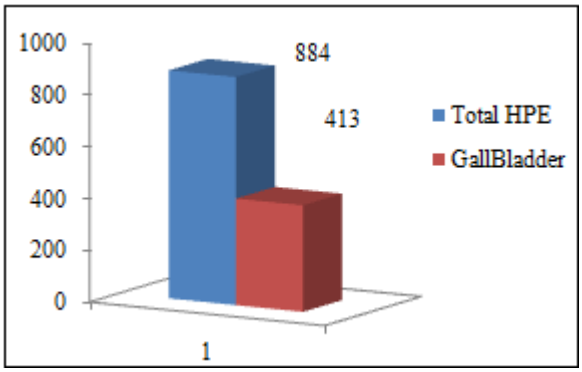
A detailed clinical history was asked whenever necessary regarding nature and duration of illness, loss of weight, significant family history, H/O smoking, dietary habits, socio-economic history and drug history, if any, was taken and noted in view of histopathological importance.

Inclusion criteria: All cases which was operated at Surgical Deptt. JMCH from Surgical Unit I-VI from Monday to Saturday and including 24 hrs emergencies during national and international holidays for gallbladder masses was accepted. Sometimes these cases was presenting as acute abdomen which requires surgery.

Exclusion criteria: Cases requested from private and nursing homes were excluded in the study.

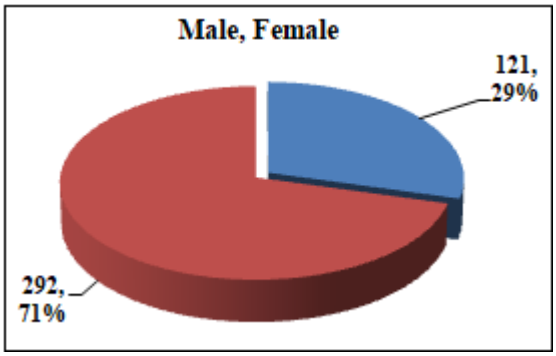
Total no. of cases received in the deptt. From Jan2020 to Dec2020 was 884, out of which the gallbladder specimen was 413.

No. of Cases	Frequency of GB mass	%
884	413	46.7%



Sex distribution at JMCH 2020

Sex	Frequency	%
Male	121	29.3%
Female	292	70.7%
Total	413	100



Month wise distribution of Sex ration at JMCH, Histopathology deptt.2020

Month	Male	Female	%
Jan	06	19	
Feb	16	33	
March	15	21	
April	07	02	
May	04	08	
June	11	21	
July	10	14	
Aug	08	02	
Sep	08	13	
Oct	15	29	
Nov	08	19	
Dec	12	28	
	121	292	

Histological types gallbladder Mass: 413

Histological types of lesions	Frequency	%
Chronic cholecystitis with cholelithiasis	145	35.1%
Chronic cholecystitis with metaplasia and cholelithiasis	12	2.9%
Adenomatous hyperplasia with cholelithiasis	15	3.6%
Adenomyomatous hyperplasia with chlelithiasis	10	2.4%
Acute on chronic cholecystitis with cholelithiasis	216	52.3%
Xanthomatous granumatous cholecystitis with cholelithiasis	13	3.14%
Adenocarcinoma carcinoma	02	0.48%
Total	413	100

Month, Age and number of Cases in the study period:

Month	25-30 yrs	31-35 yrs	36-40 yrs	41-45 yrs	46-50 yrs	51-55 yrs	56-60 yrs	Total
Jan	5	5	2	1	2	0	3	18
Feb	11	3	5	2	1	1	1	24
March	7	1	2	3	2	1	1	17
April	3	0	2	0	0	0	0	5
May	2	2	3	0	7	0	1	15
June	7	2	8	7	4	4	1	33
July	4	2	2	2	1	1	2	14
August	1	0	0	1	0	0	0	2
Sep	3	5	3	1	2	1	1	16
Oct	4	1	1	2	4	2	1	15
Nov	6	5	6	2	4	2	1	26
Dec	15	3	4	4	4	2	1	33

Description of microscopic/histological features:
Variable amount of mononuclear inflammatory cell infiltrate in lamina propia is a usual phenomena and may extend to muscularis and peri cholecystic tissue.

Morphology (**Acute cholecystitis):**
In **acute cholecystitis** the gallbladder is usually enlarged and tense, and it may assume a bright red or blotchy, violaceous to green-black discoloration, imparted by subserosal hemorrhages. The serosal covering is frequently layered by fibrin and, in severe cases, by a definite suppurative, coagulated exudate. There are no specific morphologic differences between acute acalculous and calculous cholecystitis, except for the absence of macroscopic stones in the acalculous form.

In calculous cholecystitis, an obstructing stone is usually present in the neck of the gallbladder or the cystic duct. The gallbladder lumen may contain one or more stones and is filled with cloudy or turbid bile that may contain large amounts of fibrin, pus, and hemorrhage. When the contained exudate is virtually pure pus, the condition is referred to as **empyema of the gallbladder**. In mild cases the gallbladder wall is thickened, edematous, and hyperemic. In more severe cases it is transformed into a green-black necrotic organ, termed **gangrenous cholecystitis**, with small-to-large perforations. The invasion of gas-forming organisms, notably clostridia and coliforms, may cause an acute "emphysematous" cholecystitis. The inflammatory reactions are not histologically distinctive and consist of the usual patterns of acute inflammation.

Morphology (Chronic cholecystitis)
The morphologic changes in chronic cholecystitis are extremely variable and sometimes minimal. The serosa is usually smooth and glistening but may be dulled by sub-serosal fibrosis. Dense fibrous adhesions may remain as sequelae of preexistent acute inflammation. On sectioning, the wall is variably thickened, and has an opaque gray-white appearance. In the uncomplicated case the lumen contains fairly clear, green-yellow, mucoid bile and usually stones. The mucosa itself is generally preserved.

On histologic examination the degree of inflammation is variable. In the mildest cases, only scattered lymphocytes, plasma cells, and macrophages are found in the mucosa and in the subserosal fibrous tissue. In more advanced cases there is marked subepithelial and subserosal fibrosis, accompanied by mononuclear cell infiltration. Reactive proliferation of the mucosa and fusion of the mucosal folds may give rise to buried crypts of epithelium within the gallbladder wall. Outpouchings of the mucosal epithelium through the wall (**Rokitansky-Aschoff sinuses**) may be quite prominent. Superimposition of acute inflammatory changes implies acute exacerbation of an already chronically injured gallbladder.

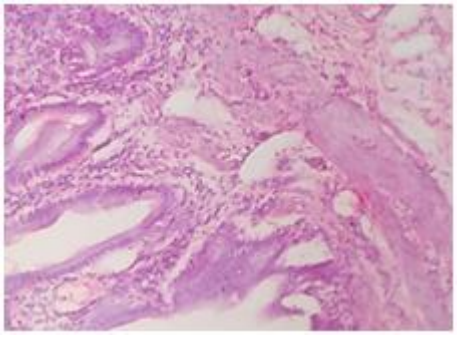
In rare instances extensive dystrophic calcification within the gallbladder wall may yield a **porcelain gallbladder**, notable for a markedly increased incidence of associated cancer.

Xanthogranulomatous cholecystitis is also a rare condition in which the gallbladder has a massively thickened wall; organ is shrunken, nodular, and chronically inflamed with foci of necrosis and hemorrhage. Finally, an atrophic, chronically obstructed gallbladder may contain only clear secretions, a condition known as **hydrops of the gallbladder**.

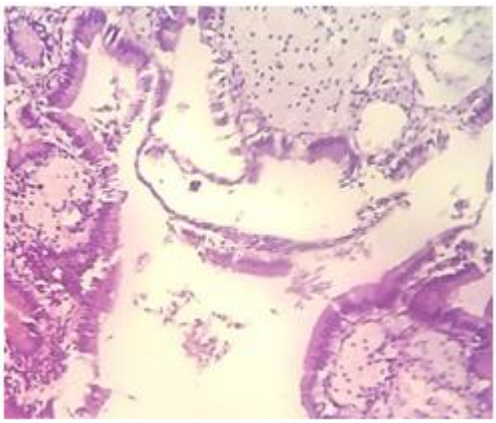
Some important variant of gallbladder lesions:
Adenomatous hyperplasia
Adenomyomatous hyperplasia:
Metaplastic changes:
IgG4 associated variant (Auto-immune):
Xantho-granulomatous type:

Differential diagnosis: (Depending upon Clinical Features):
Chronic cholecystitis does not have the striking manifestations of the acute forms and is usually characterized by recurrent attacks of either steady or colicky epigastric or right upper quadrant pain. Nausea, vomiting, and intolerance for fatty foods are frequent accompaniments.

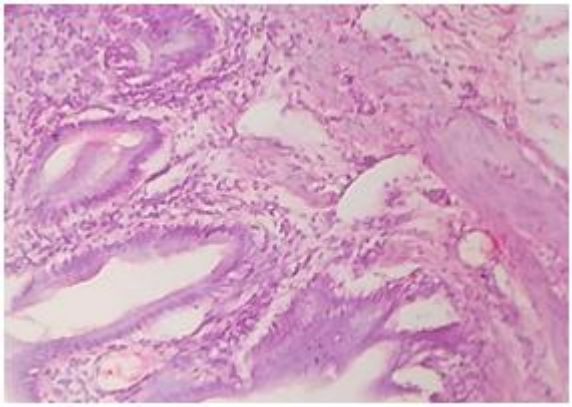
Diagnosis of both acute and chronic cholecystitis is important because of the following complications:



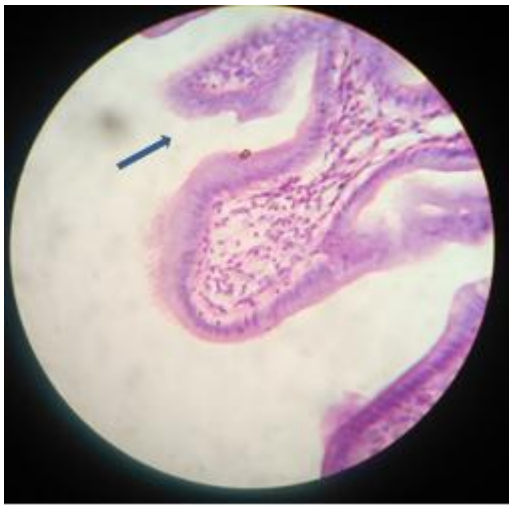
HPE showing Chronic Cholecystitis



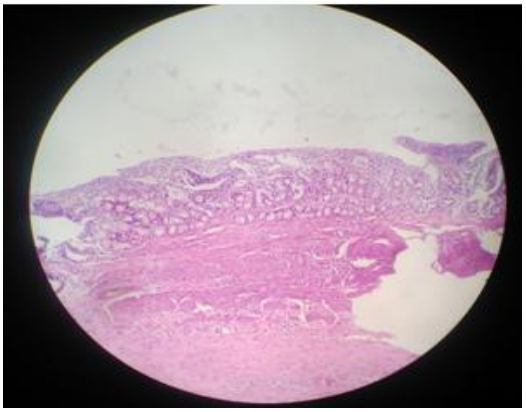
HPE showing Chronic Cholecystitis with Cholelithiasis



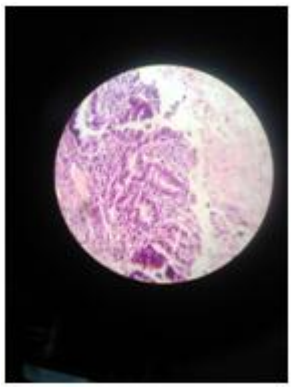
HPE showing Acute on Chronic Cholecystitis



HPE showing Xanthomatous Gallbladder



HPE showing Adenomatous Hyperplasia of Gall Bladder



Biliary enteric (cholecystenteric) fistula, with drainage of bile into adjacent organs, entry of air and bacteria into the biliary tree, and potentially, gallstone-induced intestinal obstruction (ileus).

Aggravation of preexisting medical illness, with cardiac, pulmonary, renal, or liver de-compensation

Porcelain gallbladder, with increased risk of cancer, although surveys of this risk have yielded widely discrepant frequencies.

6. Discussion

Gall bladder mass is a very common and frequent clinical finding in general surgery is concerned. Various types of gall bladder masses were operated for in different surgical setting and went on histo-pathological examination.

The estimated prevalence of cholelithiasis in India has been reported between 2% and 29%. In India, this disease is seven times more common in North than in South India. The present study was conducted to evaluate the post operated patients with gallbladder mass, cholelithiasis undergoing cholecystectomy with an aim to correlate various gallstone characteristics with morphological mucosal responses in the gallbladder.

Cholelithiasis represents one of the most frequent medical situations requiring surgical intervention. Frequently, chronic cholecystitis presents a large range of associated lesions such as cholesterolosis, muscle hypertrophy, adenomatous proliferation of the mucous glands, metaplasia, hyperplasia, and dysplasia. The last three lesions are unanimously recognized as precursor lesions with cancerous potential.

We found chronic changes in the form of acute cholecystitis and chronic cholecystitis with hyperplasia and sometimes metaplasia being more common histological finding. Similar findings have been reported in the past who reported preponderance of chronic cholecystitis in gallstone patients in their studies.

Precancerous changes of gallbladder mucosa are of particular importance for both the clinical and pathological standpoints. Improved diagnostic procedures allow recognizing invasive carcinoma more frequently at early or operable stage. However, precancerous conditions may be

overlooked by a pathologist in the lack of vision of any correlation with gallstone disease.

Stancu *et al.* and Baig *et al.*,who have reported the prevalence of hyperplasia in 7.8 and 12.5% of cases, respectively. Mechanical irritation by the calculi could be the possible explanation for these changes as proposed by Elfving *et al.*

Precancerous lesions (hyperplasia and metaplasia) although clinically seem to be more common in mixed and combined type of stones as compared to cholesterol stone, this association could not reach statistical significance (P = 0.982) on statistical analysis. Khanna *et al.*and Mathur *et al* also reported similar findings in their studies

Cholecystitis, hyperplasia, Metaplasia:

Types	Single	Double	Multiple
Cholecystitis	20	5	30
Hyperplasia	2	2	1
Cholecystitis with metaplasia	2	4	2

Association of Gallbladder mucosal response with wall thickness:

Although, Gallbladder mucosal response between precancerous conditions and gallbladder wall thickness, definitely wall thickness was >3 mm in patients with established carcinoma.

Jung *et al.* and Bazoua *et al.* also reported increased gallbladder wall thickness in carcinoma cases. We also observed that wall thickness was least in cholecystitis cases, gradually increasing in metaplasia and hyperplasia cases, and abruptly increasing in carcinoma cases.

In a study, the average size of stone (s) was found to be maximum in cases with carcinoma (4.0 cm), followed by hyperplasia (1.42 cm), metaplasia (0.88 cm), and cholecystitis (0.70 cm). This correlation between average size of the stone and type of mucosal response was found to be statistically significant.

Thus, it indicates that the average size of gallstones in cases with carcinoma was significantly more as compared to inflammation and premalignant lesions.

Lowenfels *et al.* reported that 40% of the patients with gallbladder carcinoma had stones that were more than 3 cm in size.

Vitetta *et al* and Hsing *et al.*have reported similar findings in their studies.

However, case–control studies of Roa *et al.*and Moerman *et al.* found no relationship between size and gallbladder cancer.

7. Conclusion

It can be concluded that gallbladder mass that are accompanied by gall stone or parasitic infiltration produces a major changes in the gallbladder histopathology. This is mainly due to the large size stones that excite more irritation to the mucosa in addition to the toxic effect of the lithogenic bile which produces chemical injury to the mucosa. As the exact cause-and-effect relationship cannot be substantiated with the present type of study, but surely, constant erosion of the gallbladder wall by gallstones over time constitutes an important risk factor for the development of gallbladder malignancy.

Another most important factor is gallstone number. However in some studies it could not show sufficient data to established core issue and types of stone are less important variables. The identification of premalignant modifications in the morphologic background of chronic cholecystitis is an augmenting factor in favor of **" Metaplasia-dysplasia-neoplasia"** sequence. However, being a small one year hospital based study, conclusions cannot be drawn and large multicenter study involving large population is desirable to confirm the findings.

We conclude that as the gallstone size increases, the reaction in the gallbladder mucosa changes from cholecystitis, hyperplasia, and metaplasia to carcinoma. Gallstone number and type are less important variables associated with these changes.

In our study we found that chronic cholecystitis with cholelithiasis was 35.1% which co-relate to the other national studies. At the same time number cases diagnosed as "acute on chronic cholecystis with cholelithiasis" (no.of cases 216) was 52.3% which also co-related all national as well as south East Asian literatures

Conflict Interest: it is an author own departmental study, nothing to conflict.

Financial Support: Nil

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