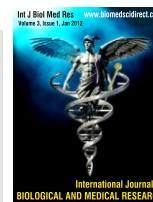




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Original Article

SPECTRUM OF HISTOPATHOLOGICAL CHANGES IN CHOLECYSTITIS

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ABSTRACT

Introduction: Diseases of the gallbladder form an important component and are in fact the bread and butter of routine surgical practice. Though traditionally considered to be a disease of middle aged obese females, the stereotype does not always apply to clinical cases as it can occur in both younger and older age groups of either sex. The histopathological picture of cholecystitis is varied and interesting for validating the clinical diagnosis and confirming the findings of ultrasonography. **Aims and objectives:** is to study the histopathology of the gallbladder in cases of cholecystitis from operative specimens and compared the tissue architecture with that of the normal gallbladder obtained from freshly donated cadavers to the Dept. of Anatomy. **Methods:** 60 specimens of gall bladder were procured from cases of cholecystitis during operation from the Dept. of Surgery at KIMS & RF, Amalapuram over a period of one year and 5 specimens of the normal gall bladder were collected from freshly donated cadavers. **Results :** In cases of cholecystitis the histological picture showed mucosal erosion/ulceration 47 cases (F=37/ M=10) with Smooth muscle hypertrophy and fibrosis present in 29 cases (25 female). Mono nuclear infiltration was the commonest histological change occurring in all layers of the gallbladder in 58 cases of which the majority were female patients (M=12/F=46). Glandular hyperplasia was present in 40 cases. Most of the cases were diagnosed by histopathological examination as chronic cholecystitis, with only two cases of acute cholecystitis and incidental findings of carcinoma in situ in three cases. Metaplastic changes were present in only 2 cases with both of them occurring in male patients. Dysplastic changes were present in 8 cases, (4 male & 4 female). Carcinoma in situ was present in 3 cases, underlining the necessity of meticulous histopathological examination in all cases of cholecystectomy. **Conclusion:** The findings of the present study will hopefully help surgeons and histopathologists to get a coherent picture of the tissue changes in cholecystitis and remain vigilant for carcinomatous changes in the gall bladder associated with long standing cholecystitis associated with gall stones.

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Introduction

The gallbladder is a fibromuscular sac which stores and concentrates bile up to ten times more than the liver bile. It reduces the alkalinity of hepatic bile and equalizes the ductal biliary pressure. When a meal (predominantly fatty) appears in the duodenum, the gallbladder contracts and the sphincter of Oddi relaxes, allowing the bile to flow into the small gut in squirts. The contraction of gall-bladder is stimulated by a hormone cholecystokinin secreted from the duodenal mucosa. The gallbladder is not indispensable, because its surgical removal is not associated with liver dysfunction.

The gallbladder is a common organ to be affected by various pathological processes. It ranges from acute cholecystitis to adenocarcinoma of the gallbladder. The presence of gallstones is an important etiological factor for two of the commonest diseases affecting the gallbladder namely acute and chronic calculus cholecystitis for which surgical removal or cholecystectomy operation is required. Diseases due to gallstones are significant for their multiplicity of presentation. A few cases of stones in the

gallbladder may remain asymptomatic throughout life without any apparent problem. Such cases have been accidentally detected during investigation for some other diseases or at autopsy. In other cases presence of stones may lead to acute cholecystitis. Repeated attacks of acute cholecystitis may result in chronic cholecystitis. Although rare, some cases may be responsible for producing carcinoma of the gallbladder. The clinical triad present in majority of cases is pain in the right upper quadrant (the pain is colicky in nature though sometimes it may be constant) along with fever and jaundice.

The aim of this present study, which is observational in nature, will be to study the histology of common gall-bladder diseases (obtained after cholecystectomy), to observe whether the changes are present in all the cases and also to note any variations from established findings. The study also aims to study the possibility of neoplastic changes in these diseases.

The specimens of the gallbladder which were used to complete this study were obtained from cases undergoing cholecystectomy for various indications. The commonest indications for cholecystectomy were - acute calculus and acalculus cholecystitis and chronic calculus cholecystitis. Apart from this, other common indications are empyema of the gall-bladder, gallbladder perforation, cholecystoenteric fistula and gallbladder neoplasms¹.

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Literature shows that histologically, the gall-bladder has got three layers - serosa, fibromuscular and mucosal layer. Some described it as a four layered structure by inserting another layer called lamina propria in between mucous and fibro muscular layer.

The gall-bladder wall microstructure generally resembles that of the small intestine. The fundus of the gall-bladder is covered by a serosa, but this only covers the inferior surface and sides of the body and neck of the gallbladder unless it is mesenteric.

Beneath the serosa is a layer of loose subserous connective tissue and adipose tissue containing large blood vessels, an extensive lymphatic network and autonomic nerves that innervate the muscularis externa and blood vessels. The connective tissue is also rich in elastic fibers and adipose tissue. Where the gall-bladder is attached to liver surface, this layer is referred to as the adventitia.

Ham's classic textbook of histology² says nothing about serosa, only to state that outside the muscle coat is a well developed perimuscular coat. This consists of loose connective tissues and may contain groups of fat cells. It conveys blood vessels, lymphatics and nerves to the organ.

The fibro muscular layer consists of fibrous tissue mixed with smooth muscle cells arranged loosely in longitudinal, circular and oblique bundles. The smooth muscle bundles are somewhat randomly oriented unlike the layered organization of the intestine. Many elastic fibres are present in the connective tissue, filling the interstices between smooth muscle bundles of this coat.³

All the authors are unanimous that the gallbladder is devoid of muscularis mucosae or sub mucosal layer. This layer contains large number of lymphocytes and plasma cells. Mucin secreting glands are sometimes seen in lamina propria of normal human gallbladder especially near its neck – but more commonly found in inflamed gallbladders.

The innermost layer i.e. the mucosa is loosely connected with the fibromuscular layer. It is yellowish brown and is elevated into minute rugae with a honey comb appearance. There are no glands in the mucosa of the gallbladder except near its neck and if the organ is distended then most (but not all) of its mucosal folds disappear. The epithelium of the mucosa is simple high columnar. The cells are provided with brush borders due to the presence of microvilli. Secretory granules have been described in apical parts of the cytoplasm of cells but the primary function of the lining cells absorptive rather than secretory. The epithelium rests on a lamina propria of loose connective tissue.⁴

What follows is a picture of the common gallbladder diseases (for which cholecystectomy operation was performed) mentioned in various standard research works.

Acute cholecystitis is clinically defined as an episode of acute biliary pain accompanied by fever and right hypochondrial tenderness and guarding, with persistence of symptoms beyond 24 hours⁵. Most of the cases (90%) are associated with gallstones. The gallbladder is usually enlarged and its wall is considerably thickened. The serosa is dull and covered with patches of fibrinopurulent exudates. A gallstone is frequently found obstructing the outflow pathway. Thick cloudy bile admixed with blood and pus fills the lumen. Histologically, an acute inflammatory reaction, characterized by edema, vascular congestion, hemorrhage, scanty to abundant neutrophilic infiltrates and necrosis predominates early in the course of this disease. As the disease evolves, lymphocytes, plasma cells, macrophages and a variable number of eosinophils appear. Granulation tissue and collagen deposition replace previously ulcerated or necrotic tissue.⁶

Chronic cholecystitis is rarely seen in the absence of lithiasis, although pure stones of the cholesterol and calcium bilirubinate types may be present without inflammation. A likely explanation for this disease is that both cholelithiasis and chronic cholecystitis are consequences of bile with an abnormal composition leading to stone formation and chemical injury to the mucosa.

The variable appearance of the gallbladder in chronic cholecystitis is a reflection of differences in the degree of inflammation and fibrosis. The gallbladder may be distended or shrunken. Fibrous serosal adhesions are suggestive of previous episodes of acute cholecystitis. On section, the wall is usually thickened, but it may be thin. Irregular shaped tubular sinuses lined by cuboidal or columnar epithelium and containing either bile or stones are present within the wall in over half of cases. These structures, traditionally known as Rokitsky-Aschoff sinuses are thought to represent herniation or diverticula resulting from increased intraluminal pressure and may extend to the muscle layer⁷. Mucosal erosions or ulcers are frequently found in association with impacted stones. The presence of gall stones is not sufficient or necessary for the diagnosis of chronic cholecystitis. The diagnosis is based on the demonstration of a predominantly mononuclear infiltrate, fibrosis and metaplastic changes.

The degree of the inflammatory reaction is variable. In some cases, the infiltrate is exclusively located in the mucosa, whereas in others it extends into the muscularis and serosa. Most of the cells are mononuclear; lymphocytes usually predominate over plasma cells and histiocytes. When neutrophils are predominantly found within the epithelium in a setting of chronic cholecystitis, it is preferable to view them as evidence of “ activity ” of the inflammatory process rather than as a mixed acute and chronic or subacute condition. The term chronic active cholecystitis may better define these cases.

As a result of chronic injury, metaplastic changes can result⁸. The surface epithelium frequently undergoes metaplasia of superficial gastric type. Less frequently, intestinal metaplasia may occur and is identified by the appearance of cells with intestinal phenotypes such as goblet cells, absorptive columnar cells, Paneth cells and gut endocrine cells. Very infrequently squamous metaplasia may be found.

Gallbladder carcinoma is an uncommon malignancy occurring mainly in the elderly population, with a 3:1 female to male predominance. Majority of cases are associated with gallstones; chronic gallstone disease and resultant dysplasia have been cited as a causative factors⁹. About 98% of gallbladder carcinomas are adenocarcinomas, with squamous cell carcinoma and metastases accounting for the rest.

MATERIALS & METHODS

For the present study, 60 cholecystectomy specimens of the gallbladder were collected from the departments of surgery of Konaseema Institute of Medical Sciences & Research Foundation, Amalapuram for a one year.

Pre operative ultrasonological (USG) reports of the patients were collected from their treatment sheets and digital photographs were taken. The USG reports were studied for data regarding presence/absence of stones, gallbladder wall thickness, dimensions etc.

At the same time, a histological study of normal gallbladders was done from five specimens collected from freshly prepared cadavers obtained from the Department of Anatomy, Konaseema Institute of Medical Sciences & Research Foundation, Amalapuram.

During cholecystectomy, the gallbladder after its removal was collected in 10% buffered formol saline and was studied as follows

Morphological changes: - The external appearance of the gall bladder, its shape, size presence/absence of stone(s) and also the type namely: pigmented, cholesterol or mixed type.

Histological changes: - The specimens were washed with normal saline, its contents collected separately and the inner surface observed for different changes. Pieces of tissue (5mm×5mm) were taken from the fundus, body and neck of the gallbladder and were processed using automatic tissue processor (LEICA TP 1020).

Paraffin blocks were prepared and stained with hematoxylin and eosin and examined under the microscope. The slides were studied and photographed using digital photographic microscope.

For recording of data from pathological gallbladders, the following criteria were used:-

Hyperplasia - Pseudostratification of epithelium, nuclear crowding, tall columnar cells, and occasional mitotic figures.

Dysplasia - Pseudostratification of epithelium, nuclear crowding, some loss of architecture, disorganization of epithelium, nuclear atypia.

Intestinal metaplasia - Presence of goblet cells.

Antral metaplasia - Branched tortuous glands in lamina propria.

Carcinoma in situ - Hyperchromatic nuclei having one or more prominent nucleoli, eosinophilic cytoplasm, clear or mucous secreting, occasional giant cells, loss of cell polarity, atypical mitotic figures, absence of stromal invasion.

All the relevant findings were observed and noted and statistical representations of these findings were made.

RESULTS

Morphological changes in cholecystectomy specimens

The gall bladder was found to be shrunken in maximum number of cases – 40 (66.67%) with 12 (20%) specimens having normal flask shape, whereas 8 (13.3%) specimens were distended.

The mean length of the gall bladder was 8.3 cm (range 6-12cm) with the maximum number of cases (19) in the 7-8 cm range.

The mucosa was elevated into multiple small folds or rugae which gave the interior of the gallbladders a honey comb appearance.

Stones were present in the maximum number of cases (59) but their number or type did not have any bearing on the gross changes.

The serosal surface of the gall bladder was normal in 12 (20%) cases while adhesions were present in 48 (80%) specimens.

Histological features in anatomical specimens of the gallbladder

Histologically, the walls of the gallbladder specimens had three layers - serosa, fibro muscular layer, lamina propria and mucosa.

Serosa – This layer consisted of fibrous tissue and a thin layer of flattened epithelium. Beneath it was a layer of sub serous loose connective tissue.

Fibromuscular layer – this layer was composed of fibrous tissue mixed with smooth muscle arranged loosely in longitudinal, circular and oblique bundles. Most of the muscle fibres ran obliquely. The fibrous tissue filled up the interstices between smooth muscle bundles.

The smooth muscle bundles were somewhat randomly oriented unlike the layered organization of the intestine.

All the gall bladder specimens were devoid of muscularis mucosae or sub mucosal layer.

The loose connective tissue beneath the mucosa is best described as a lamina propria. It was rich in capillaries and small venules. It contained large number of lymphocytes and plasma cells. Mucin secreting glands were sometimes seen in lamina propria in sections near the neck.

The epithelium of the mucosa was tall columnar. Each cell resembled the one beside it. They were provided with a brush border due to microvilli.

In addition, deep diverticula of the mucosa called Rokitansky-Aschoff sinuses sometimes extended through the muscularis externa (Fig.1). They are thought to precede pathologic changes. Bacteria may accumulate in the sinuses causing chronic inflammation. Their prominence in the settings of inflammation and the gall stone formation suggests that they are acquired herniations of the mucosa.

Histological changes in cholecystectomy specimens

Mono nuclear infiltration was the commonest histological change occurring in 58 cases (96.67%) (Fig.2). Again the majority were female patients (M=12/F=46) below 45 yrs of age.

Glandular hyperplasia was present in 40 (66.67%) cases with the majority occurring in females (33 cases).

Dysplastic changes were present in 8 (13.33%) cases, with 4 male and 4 female patients. These changes were observed in patients more than 45 yrs of age (Fig.3).

Out of the 60 gall bladder specimens examined, metaplastic changes were present in only 2 (3.33%) cases with both of them occurring in male patients (Fig.4).

Only 3 (5%) cases of carcinoma in situ were present, with all the cases occurring in females above 45yrs of age (Table 1).

Fig.1 The slide shows all the layers of a gall bladder. The characteristic feature that has been focused in this slide is the presence of Rokitansky-Aschoff sinuses extending even through the fibromuscular layer.

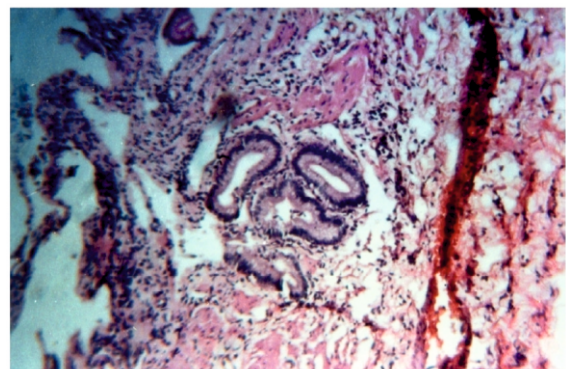


Fig.2 It is a high power photomicrograph (H & E x 40) of cross section through the body of the gall bladder of an adult female. The section was stained with haematoxylin and eosin. The slide shows the following features –

There is extensive mononuclear infiltration in all the layers of the gall bladder, i.e. lamina propria, fibromuscular layer and perimuscular layer. Extravasated red blood corpuscles are seen in the lamina propria and within the fibromuscular layer. There is no change in the columnar epithelium of the mucous membrane. Smooth muscle hypertrophy can also be well appreciated in the given slide.

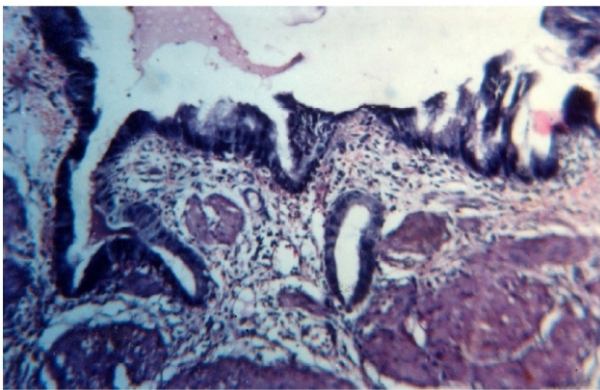


Fig.3 It is a high power photomicrograph (H & E x 40) of cross section through the fundus of the gall-bladder in an adult male. The section was stained with haematoxylin and eosin. The features presenting in the slide are as follows:-

Dysplastic changes are seen in the epithelium of the mucous membrane, characterized by deep staining nuclei and loss of polarity. There is loss in the uniformity of individual cells as well as loss in their architectural orientation. The nuclei are large compared to the size of the cell. Basement membrane remains intact. Dysplastic changes are seen in one Rokitansky- Aschoff sinus within the field. Mononuclear infiltrations are also visible.

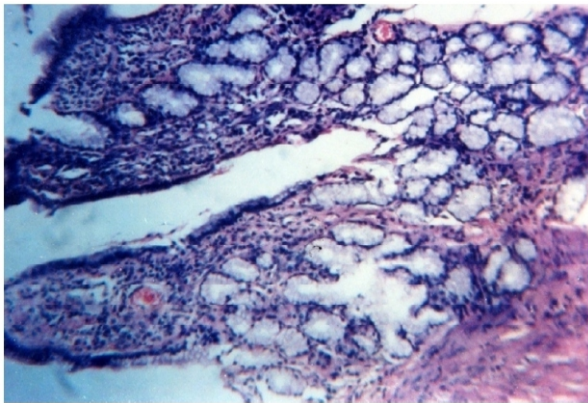


Fig.4 It is a high power photomicrograph (H & E x 40) of cross section through the body of the gall bladder in an adult female. The section was stained with haematoxylin and eosin. The features presenting in the slide are as follows -

Besides presence of numerous mononuclear cells in the lamina propria, there is glandular hyperplasia in the layer. The glands are mucin secreting in type. Small blood vessels

are visible in the mucous folds. Dysplastic changes are seen in the epithelial cells characterized by loss of polarity of nuclei, deep staining nuclei etc. although basement membrane is remaining intact. Metaplastic changes in the epithelial layer are also seen.

Table 1. Age and sex distribution of the different histological changes observed.

Histological changes	Total no. of cases	Sex	Age	Percentage
METPLASIA	2	M=2 / F=0	Ø=1 / ©=1	3.33%
DYSPLASIA	8	M=4 / F=4	Ø=1 / ©=7	13.33%
CARCINOMATOUS CHANGES	3	M=0 / F=3	Ø=0 / ©=3	5%
GLANDULAR HYPERPLASIA	40	M=7 / F=33	Ø=23 / ©=17	66.67%
MONO NUCLEAR INFILTRATION	58	M=12 / F=46	Ø=38 / ©=20	96.67%
SMOOTH MUSCLE HYPERTROPHY	29	M=4 / F=25	Ø=19 / ©=10	48.33%
FIBROSIS	58	M=12 / F=46	Ø=38 / ©=20	96.67%
MUCOSAL EROSION/ULCERATION	47	M=10 / F=37	Ø=33 / ©=14	78.33%

M -- male

F -- female

Ø -- age less than 45 yrs.

©-- age more than 45 yrs

DISCUSSION

Sections of the normal gall bladder were studied in five specimens. All of them showed similar histological features. The surface cells of mucous membrane of most of the specimens were denuded as they were collected from cadavers. This change occurred although the specimens were collected in winter and within earliest possible time after death and embalming. This is probably due to the corrosive action of bile on mucous membrane after death. This is corroborated with Judd and Burden¹⁰ who observed that in some specimens the mucous membrane had disappeared within an hour after death.

Out of the 60 pathological gall bladder specimens, 46 were from female and 14 from male patients (M: F=1:3.3). The mean age of patients was 39.3yrs (range 16-66), with the maximum number of cases in the 40-49 yrs age group. All the patients except one complained of upper right quadrant/epigastric pain with only 10 patients having fever. Jaundice was an uncommon clinical feature being present in only 10 cases. Stones were present in 59 cases with the mixed variety being the commonest (88.1%) followed by cholesterol (10.2%) and pigment (1.7%) stones.

Two cases were diagnosed to be acute cholecystitis. The gall bladder wall was edematous with leucocyte infiltration, vascular congestion and scattered abscess formation. Rest of the specimens had chronic cholecystitis. The mucosa and subserous fibrous tissue was infiltrated with lymphocytes, plasma cells and

macrophages. This was followed by fibrosis of the sub serosal and sub epithelial layers with mononuclear infiltration. Fusion of the mucous folds created epithelial crypts while outpouching of the mucosa into the gall bladder wall formed Rokitansky Aschoff sinuses, some of which contained gallstones.

The gall bladder was found to be shrunken in maximum number of cases – 40 (66.67%) with 12 (20%) specimens having normal flask shape, whereas 8 (13.3%) specimens were distended.

The mean length of the gall bladder was 8.3 cms (range 6-12cms) with the maximum number of cases (19) in the 7-8 cms range.

Stones were present in the maximum number of cases (59) but their number or type did not have any bearing on the gross changes.

The serosal surface of the gall bladder was normal in 12 (20%) cases while adhesions were present in 48 (80%) specimens.

The epithelium of mucous membrane was eroded / ulcerated in most of the cases (47). This is in accordance with the findings of Mittal et al, 2010¹¹ which state that mucosal erosions and ulcerations are frequently found in association with impacted stones.

In a few cases (8), dysplastic changes were seen characterized by loss of uniformity of individual cells as well as loss of their structural orientation, loss of polarity and deep staining nuclei. Due to loss of polarity, the epithelium got a look of pseudostratification. Liatio M¹² studied 71 cholecystectomy specimens and found dysplastic changes in 24 of them.

Metaplasia was seen in 20 of these and 14 arose within dysplastic portion.

The reported incidence of dysplasia varies in different studies according to the number of sections examined and the criteria chosen for histological diagnosis.

Glandular hyperplasia was observed in 40 cases (66.67%). They were mucin secreting in type, limited to lamina propria and present in even those sections which were taken from fundus and body of the gall bladder. They were lined by cuboidal epithelium. Of these 40 cases, 4 had hyperplastic as well as dysplastic changes while 3 cases carcinoma in situ as well.

Khanna R¹³ also observed that hyperplasia was commoner than dysplasia and metaplasia and found it in 60% of the gall bladder specimens of their study. They observed that in 20% hyperplasia was associated with metaplasia and in 6% with dysplasia.

Albores – Saavedra et al¹⁴ suggested that in a small number of cases, hyperplasia of the gall bladder evolves towards atypical hyperplasia and that this may progress to in situ carcinoma which finally becomes invasive carcinoma.

Fibrosis was observed in 58 cases. It was one of the commonest changes found in the present study. However it was not present uniformly in all the layers. In some cases it was present in the lamina propria, in some cases in the perimuscular layer and in others it was present in varying combinations in all the three layers.

Mononuclear infiltration was also one of the commonest histological changes that we found in our study (58 cases). This change was present in all the lamina propria, fibromuscular and perimuscular layers. The density of infiltration however was not the same in all the layers and varied from case to case.

Smooth muscle hypertrophy was another change that we came across in our study (29 cases), although it was not as common as fibrosis, hyperplasia or mononuclear infiltration. Some of the slides even showed the same thickness of the muscular layer as compared to the normal studies.

Rokitansky-Aschoff sinuses were found in some of the sections in the lamina propria. Some even penetrated the fibromuscular layer. However gall bladders having pigment stones were devoid of Rokitansky-Aschoff sinuses. Similar observations were made by Baig SJ et al¹⁵, that Rokitansky-Aschoff sinuses were not seen in the gall bladder containing pigment stones but were seen in gall bladders containing mixed and cholesterol stones.

Regarding the carcinomatous changes, only 3 cases of carcinoma in situ were found. All the three cases were female and were above 45yrs of age. Gallbladder carcinoma (most commonly adenocarcinoma) is usually associated in patients with gallstones and chronic cholecystitis, it is usually more common in women than in men. Gallbladder specimens in all the three cases were distended with surface adhesions. On dissecting the specimens, two of them had cholesterol stones.

Gall stones are the most important risk factor in the development of gall bladder carcinoma. According to Piehler JM¹⁶, gall stones are found in 65-90% of patients with gall bladder carcinoma. Hart et al¹⁷ states that frequencies of gall stones and gall bladder carcinoma run parallel in a defined population. Autopsy data from Chile had suggested that the risk of gall bladder carcinoma is seven times greater in the presence of gall stones compared to the risk of those without stones¹⁸. There is however no association of gall bladder carcinoma with any specific type of stones.

Stones were present in 59 out of 60 cases, with 52 patients (88.1%) having mixed stones, 6 patients (10.2%) cholesterol stones and only 1 patient (1.7%) having pigment stones. Baig SL et al¹⁵ in their study observed that out of 40 patients, 28 had mixed, 8 had pigment whereas 4 had cholesterol stones.

The presence of stones emphasize the point that its presence is significant if not absolute in the pathogenesis of cholecystitis (both acute as well as chronic). The study also indicated that the histological changes of gall bladder in cases of cholesterol or pigment stones were the same as those in case of mixed stones, the most commonly occurring gall stone. There was no specific characteristic change which may indicate the type of stone, mixed, cholesterol or pigment type.

Out of the 60 cases however, 2 specimens had no gallstones but were confirmed by histological examination to be suffering from chronic cholecystitis.

CONCLUSION

To conclude, there are various gall bladder diseases for which cholecystectomy (either open or laparoscopic) is required, but still the commonest indication is chronic cholecystitis.

Gall bladder pathology is more common in females than in males and affects people mainly in the fourth and fifth decades of life. There is a positive correlation between ultrasonological with morphological and histological changes in the gall bladder in various pathologies; specially acute and chronic cholecystitis. However variations might occur taking into account the operator bias. Mononuclear infiltration and fibrosis are the commonest histological changes observed followed by glandular hyperplasia and mucosal erosions and ulcerations.

Regarding gallstones, mixed types are the commonest to be observed. Gallstones are important but not an absolute factor in the pathogenesis of gall bladder carcinoma. This study could show no difference in the histological changes based on either the number or the nature of the gall stones. Finally hyper plastic as well as dysplastic changes as observed, are the precursor lesions of gall bladder carcinoma and these cases should be followed up for a prolonged period. All traces of malignant spread should be thoroughly investigated and be treated accordingly¹⁹ and so it has also been argued that all gall bladders containing stones should be removed surgically because of the risk of cancer, risk being greater than the operative mortality²⁰.

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