Original Paper

The Frequency of Gall Bladder Pathology in Consecutive 576 Cholecystectomies

Layth A. Alshareefi^, Mohammed A. Ali^, Nazar J. Metib^*, Mahdei Jasim^

^AL-Hussein teaching hospital-Iraq-Karbala."Jan.2018

Abstract

Background: Cholecystectomies with relevant frequency of gall bladder pathologies is not clear.

Patients and methods: Throughout 2016 and 2017 in pathology unites of two hospitals, 576 cholecystectomy cases were analysed. The age of the patients range from 2 to 80 years with a mean of 42.60±15.62 years. Male to female ratio was 152:424 (1:3).All the samples reviewed by two consultant pathologists.

Aim of study: To Study the frequency of histopathological changes in 576 cholecystectomies.

Results and discussion: Of the total sample which was 576, 437 cases (75.9%) had gall stones, 51 cases (8.9%) were acute cholecystitis, 464 cases (80.6%) were chronic cholecystitis, 9 were malignant (1.6%) and 52 were normal (9%). All the malignant cases were solid variant adenocarcinomas and only one was metastatic from sigmoid colon. Acute suppurative cholecystitis were seen in 24 cases (4.1%), xanthogranulomatous cholecystitis 34 (6.1%), Rokitansky – Aschoff sinuses were seen in 223 (38.7%), inspissated bile 24 (4.2%), adenomyomatous changes 146 (25.3%), focal abscess formation 26 (4.5%), cholesterosis 31 (5.4%), metaplasia 465 (80.7%), single adenomatous polyp, eosinophilic cholecystitis 25 (4.3%).

In adenomyomatous changes the epithelial proliferation was florid with Rokitansky – Aschoff sinuses and smoth muscle hypertrophy. Metaplastic changes were of pyloric, intestinal and mucous glands types, the adenomatous polyp was of biliary type with low grade epithelial atypia.

Conclusion: The available data may provide basic knowledge of the gall bladder pathology in holey Karbala.

Keywords: Gallbladder, histopathology, cholecystectomy.

Introduction

Gall bladder

Gallbladder is a hollow organ that sits just beneath the right lobe of the liver[1]. In adults, the gallbladder measures approximately 8 centimeters in length and 4 centimeters in diameter when fully distended [1]. And has a capacity of about 100 milliliters [2].

It opened into the biliary tree and the cystic duct. Anatomically, the gallbladder is divided into three parts: *fundus*, *body*, and *neck*. The cystic duct unites with the common hepatic duct to become the common bile duct. At the junction of the neck of the gallbladder and the cystic duct, there is an out-pouching of the gallbladder wall forming a mucosal fold known as **Hartmann's pouch**, where gallstones commonly get stuck [3].

The gallbladder mucosa is lined by a single layer of simple columnar epithelium with an apical brush border of microvilli, very similar to intestinal absorptive cells [4]. A distinctive feature of the gallbladder anatomy is the presence of Rokitansky-Aschoff sinuses, which are deep outpouchings of the mucosa that can extend through the muscular layer [5,6] .

Underneath the epithelia is an underlying lamina propria and unlike intestine gall bladder has no muscularis mucosae layer .The muscular layer, formed by smooth muscular tissue .The interspersed muscle fibres lie in

*for correspondence email: dr.nazarj@gmail.com

longitudinal, oblique and transverse directions and are not arranged in separate layers . The serosa is a thick layer that covers the outer surface of the gallbladder, and is continuous with the peritoneum, which lines the abdominal cavity. The serosa contains blood vessels and lymphatics [2,5].

The main purpose of the gallbladder is to store bile needed for the digestion of food. When food containing fat enters the digestive tract, it stimulates the secretion of cholecystokinin (CCK) from I cells of the duodenum and jejunum. In response to cholecystokinin, the gallbladder rhythmically contracts and then releases its contents into the duodenum. The bile emulsifies fats in partly digested food, thereby assisting their absorption. Bile consists primarily of water and bile salts, and by that it also acts as a means of eliminating bilirubin, which is a product of hemoglobin metabolism from the body.[7]

One of the common gall bladder diseases include gall stone formation. The term cholelithiasis refer to the presence of stones in the gallbladder or to the diseases caused by gallstones [8]. Most people with gallstones (about 80%) never have symptoms [9].

In 1–4% of patients with gallstones, a crampy pain in the right hypochondrial area, occurs each year. Complications of stones include inflammation of the gallbladder (cholecystitis), inflammation of the pancreas, and liver. Symptoms of these complications may include pain of more than five hours duration, fever, jaundice, vomiting, or tea-color urine. Risk factors for gallstones include birth control pills, pregnancy, family history of gallstones, obesity, diabetes, liver disease, or rapid weight loss. Gallstones are formed in the gallbladder, typically from either cholesterol, bilirubin or mixed. Diagnosis is typically confirmed by ultrasound [10].

Women more commonly have stones than men and they occur more commonly after the age of 40. Pigmented gallstones are most commonly seen in the developing world with a risk factors like hemolytic anemias (sickle-cell disease and hereditary spherocytosis), cirrhosis, and biliary tract infections [11].

Cholecystitis is an inflammation of the gallbladder which include acute and chronic ones [12,13]

On physical examination, fever is common A gallbladder with cholecystitis is almost always tender to touch [9,10]. Pain with deep inspiration leading to termination of the breath while pressing on the right upper quadrant of the abdomen usually causes pain (Murphy's sign) [13].Yellowing of the skin (jaundice) may occur but is often mild. However severe jaundice suggests another cause of symptoms such as choledocholithiasis [14].

Gallstones are the most common cause of gallbladder inflammation but it can also occur due to blockage from a tumor or scarring of the bile duct [15].

Gallstones blocking the flow of bile account for 90% of cases of acute calculous cholecystitis [13,15].Blockage of bile flow leads to thickening and buildup of bile causing an enlarged, red, and tense gallbladder [13].The gallbladder is initially sterile but often becomes infected by bacteria, predominantly *E. coli*, *Klebsiella*, *Streptococcus*, and *Clostridium* species. Inflammation can spread to the outer covering of the gallbladder and surrounding structures such as the diaphragm, causing referred right shoulder pain [10].

A calculous cholecystitis is typically seen in people who are hospitalized and critically ill. Males are more likely to develop acute cholecystitis following surgery in the absence of trauma [11,13]. It is associated with many causes including vasculitis, chemotherapy, major trauma or burns [15].

Ultrasound or computed tomography often shows an immobile, enlarged gallbladder.[10]

Grossly; Enlarged, distended gallbladder with congested vessels (“angry red color”), serosal and mucosal exudates and thickened wall with edema and hemorrhage. Ulcers with blood clot, pus and bile may be seen [11].

Microscopically; initially edema, congestion, hemorrhage, fibrin deposition in and around muscular layer,later mucosal and mural necrosis with neutrophils. Variable reactive epithelial changes resembling dysplasia and finally myofibroblastic proliferation with chronic inflammatory infiltrate seen [15].

Treatment involves immediate antibiotics and cholecystectomy within 24–72 hours [16] . Chronic cholecystitis occurs after repeated episodes of acute cholecystitis and is almost always due to gallstones [14] .It may be asymptomatic or present with severe symptoms of acute cholecystitis and may lead to a number of complications such as gangrene, perforation, or fistula formation [10,11] .

The diagnosis of chronic cholecystitis is suggested by the history (abdominal pain, nausea, vomiting, and fever) and physical examinations in addition to laboratory tests and ultrasonographic examination [17] . Grossly; variable thickening of gallbladder wall and variable adhesions .While microscopically; Mild chronic inflammation with Rokitansky-Aschoff sinuses, granulomas (from ruptured Rokitansky-Aschoff sinuses), smooth muscle hypertrophy. Neuromatous hyperplasia, hyalinized collagen, dystrophic calcification, lymphoid aggregates (5%). Variable mucosal changes (normal, atrophic, ulcerated) and Variable metaplastic change [18] .

For most people with acute cholecystitis, the treatment of choice is surgical removal of the gallbladder [19] . Laparoscopic cholecystectomy is performed using several small incisions located at various points across the abdomen. Several studies have demonstrated the superiority of laparoscopic cholecystectomy when compared to open cholecystectomy. People undergoing laparoscopic surgery report less incisional pain postoperatively as well as having fewer long term complications and less disability following the surgery[20,21]. Additionally, laparoscopic surgery is associated with a lower rate of surgical site infection [22] .

Untreated cholecystitis can lead to worsened inflammation and infected bile that can lead to a collection of pus surrounding the gallbladder, also known as empyema [10] .

Strawberry gallbladder comes from the typically stippled appearance of the mucosal surface on gross examination, which resembles a strawberry[23]. Cholesterosis results from abnormal deposits of cholesterol esters in macrophages within the lamina propria (foam cells) and in mucosal epithelium. May be patchy localized form or in a diffuse form [24] .

Polypoid growths or lesions in the wall of the gallbladder include cholesterol polyp cholesterosis, adenomyomatosis, adenomas and adenocarcinoma .Most small polyps (less than 1 cm) are not cancerous and may remain unchanged for years. Larger polyps are more likely to develop into adenocarcinomas[25] .

Cholesterol polyps, account for most benign gallbladder polyps [26].

Adenomyomatosis encounters two types: (a) numerous Rokitansky-Aschoff sinuses accompanied by smooth muscle hyperplasia and (b) extensively fibrotic gallbladder wall with numerous Rokitansky-Aschoff sinuses but few/no smooth muscle bundles and both types have an expanded subserosal layer containing abundant nerve-trunks; surface epithelium may be papillary [26] .

Mucosal epitheial metaplasia classified as pyloric, intestinal, foveolar and biliary. Intestinal subtypes includes tubular, papillary and tubulopapillary. By definition, contains at least low grade dysplastic epithelium and found in 0.5% of cholecystectomy specimens, usually asymptomatic. Increased prevalence found with familial adenomatous polyposis or Peutz-Jeghers syndrome and 70% are women. Carcinoma within adenoma found in 23% , but invasive carcinoma rare if < 1 cm [27,28].

Pyloric gland adenoma can progress to carcinoma with invasion and fatal outcome. Grossly; 3-25 mm polypoid structure projecting into lumen, may be sessile and 90% are single [29]. Microscopically; biliary adenoma: composed of columnar cells similar to normal biliary cells of gallbladder. Foveolar adenoma: has low-grade dysplasia. Pyloric gland adenoma: usually tubular with pyloric gland features; squamoid morules in 28% and high grade

dysplasia common in pyloric and intestinal adenomas[29] .

Cancers of the biliary tract classified as cholangiocarcinoma (cancers arising from the bile duct epithelium), ampulla of Vater cancer, and gallbladder cancer. All subtypes of biliary tract cancers are rare and have an overall poor prognosis. They are also difficult to diagnose [30].

Gallbladder cancer is the fifth most common gastrointestinal (GI) cancer in the United States. Worldwide, it is the sixth most common GI cancer and the most common biliary tract malignancy, accounting for 80%–95% of biliary tract cancers [31].

The tumor is usually located in the fundus of the gallbladder. Local spread through the gallbladder wall can lead to direct liver invasion, or, if in the opposite direction, leads to transperitoneal spread (20% of patients at presentation), with implants on the liver, on the bowel, and in the pelvis. Tumor may also directly invade other adjacent organs such as the stomach, duodenum, colon, pancreas, and extrahepatic bile duct. [32,33].

At the time of diagnosis, the gallbladder is often replaced or destroyed by the cancer. In addition, approximately 50% of patients have regional lymph node metastases[34] .

Materials and methods

This is a retrospective study involved microscopic revisions of formalin fixed paraffin embedded tissue sections obtained from consecutive 576 cholecystectomy specimens in one and halve year period, 2016 and halve of 2017 in both Al-Hussein teaching hospital and Al-Kafeel private surgical hospital, histopathology laboratory unite, revision was made by two consultant pathologist ,no significant interobserver variability seen on revision. The average number of gross sections per case was 3 - 4 pieces including fundus, body, neck and any abnormal gross area, tissue processing was automated through Leica and Thermo companies' devices and Olympus D72 camera used for photo capturing. Clinical data regarding presentation, age, sex and elective or emergency surgery were retrieved from the patients archive forms. The data had been analyzed by SPSS statistical system with Chi square and p value was calculated.

Results

A total of 576 consecutive cholecystectomies were reevaluated histologically. The age of patients ranged from 10 years to 80 years with a mean of 42.60 ± 15.62 years. Male to female ratio was 152:424, 437 out of 576 histological samples (75.9%) had gall stones. The type of gall stones was not described or analyzed chemically; as most of them discarded and even their colours not mentioned. The reason for cholecystectomies was acute cholecystitis in 51 cases (8,9%), chronic nonspecific cholecystitis in 464 cases(80.6%), calculous cholecystitis seen in 437 cases(75.9%), gall bladder carcinoma in 9 cases (1.8 %) , and cholecystectomy of clinically stable gall bladder as elective surgery for gall stones, in hemolytic diseases and congenital anomalies of biliary tree in 52 cases (9%). All of the malignant cases were of adenocarcinomas (Table 1).

Acute cholecystitis was found in 51 (8.9 %) cases. No acute perforation of the gall bladder was detected. (fig.1)

Eosinophilic cholecystitis was present in 25 cases (4.3%).

Follicular cholecystitis present in this series in a percentage of 5.6% (32 cases) (fig.3).

Rokitansky-Aschoff sinuses (RAS) (Figure 4) were recognized in 223 cases (38.7%) with chronic cholecystitis cases. The presence of microliths or inspissated bile within RAS was recognized in 24 cases (4.2 %) of the 223 cases. Foreign body granulomatous reaction was present around the microliths or inspissated bile in 5 cases.

Adenomyomatous changes (Figure 4) were present in 146 cases (25.3%).

Metaplastic changes were present in 100 cases (17.3%) (table 2), include pyloric gland metaplasia (Figure 5) which was recognized in 53 cases (9.2%). Intestinal metaplasia was recognized in 24 cases (4.2%) and formed by presence of long mucous secreting epithelial lining with occasional goblet cells.Mucous gland metaplasia present in 23 cases (4%).

Table 1. Frequency of pathological reasons.

	Frequency	Percentage
Normal	52	9.0
acute	51	8.9
chronic	464	80.6
Malignant	9	1.6
Total	576	100.0

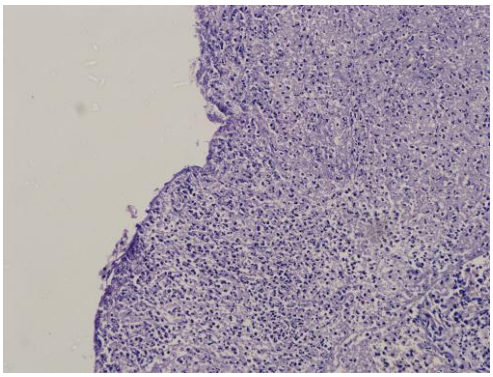

Figure 1. acute cholecystitis, large number of neutrophils with abscess. H&E 200x.

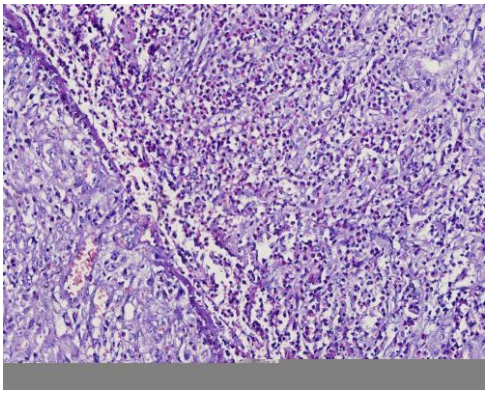

Figure 2. eosinophilic cholecystitis,large number of eosinophilic infiltration seen(>100 cell/HPF), 200x.

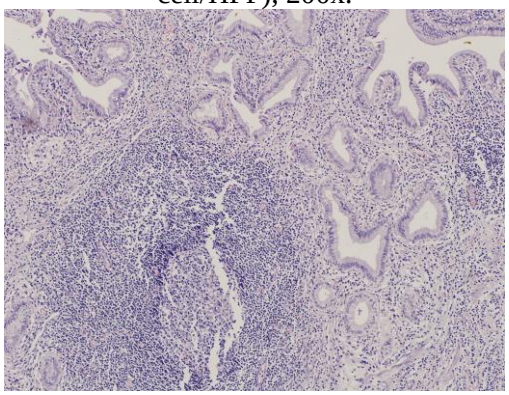

Figure 3. chronic follicular cholecystitis,reactive lymphoid follicle seen,H&E 200x

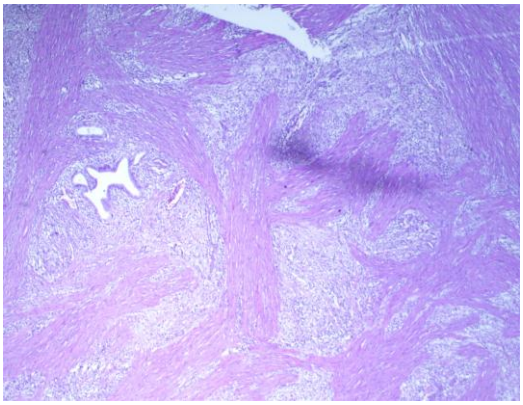

Figure 4. RAS and adenomyomatous change,thick muscular layer,H&E 100x.

Table 2. percentage of metaplastic changes.

Total case		No. of samples	Percentage
negative for metaplasia		476	82.6%
Positive for Metaplasia	Pyloric	53	9.4%
	Intestinal	24	4.2%
	Mucous	23	4%
Total		576	100%

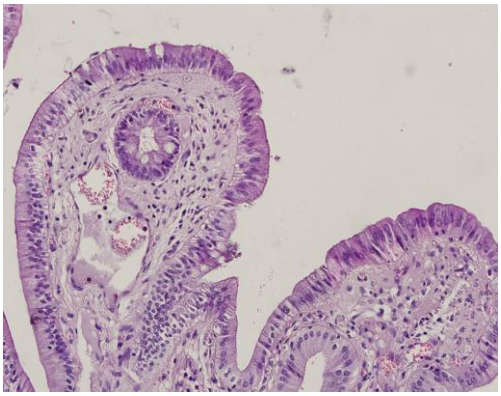

Figure 5. Intestinal metaplasia, villous morphology with few goblet cells, H&E, 100x.

Xanthogranulomatous cholecystitis (Figure 6) was noted in 35 cases (6.1%). Focal abscess formations were noted in 26 cases (4.5%).

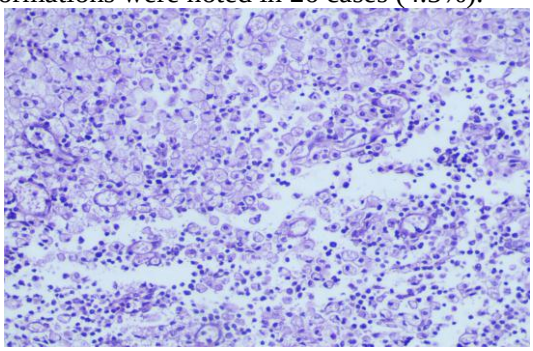

Figure 6. xanthogranlomatous cholecystitis,large number of foamy histiocytes with mixed acute and chronic inflammatory cells.200x.

Cholesterosis was identified in 31cases (5.4%). All cases of cholesterosis were associated with chronic cholecystitis, only 12 cases (2.1%) of cholesterosis presents as cholesterol polyps.

Adenomas of villous or tubular type (Figure 7) were demonstrated in only single case and was of tubular adenoma (0.2%). It was subjected for frozen section and result of benign adenomatous polyp was obtained, latter on perminant section it was found to be tubular adenoma,charecterized by adenomatous proliferation of biliary type epithelium with low grade atypia.

Invasive adenocarcinoma (fig.8) was recognized in 9 cases (1.8%). All of these, were tubular and solid glandular non mucinous and non-papillary adenocarcinomas.All the cases were invasive and reached muscularis layer except one case invading deeply to the serosal fat. Of these 9 carcinomas, two were incidental findings in pathologic examination. The surgical margins were negative in all the 9 cases. The pathological stage was pT1b in 8 cases, and pT2 in 1 case.

Discussion

The histopathological features and incidence of gall bladder lesion varies depending on races, countries, and institutes. It is well known that gall bladder diseases affect more frequently women than men [34]. The gall bladder disease most frequently occurs in middle age population. The present data are compatible with the data of Tadashi Terada et al [35,38].

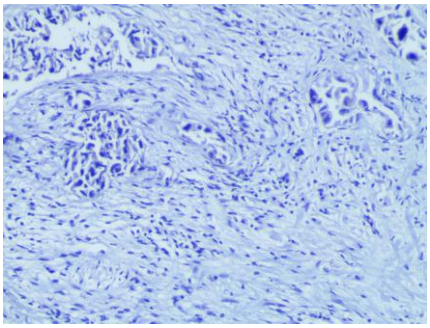

Figure 8. Gall bladder adenocarcinoma, malignant epithelial nests deep in muscularis layer H&E,20x.

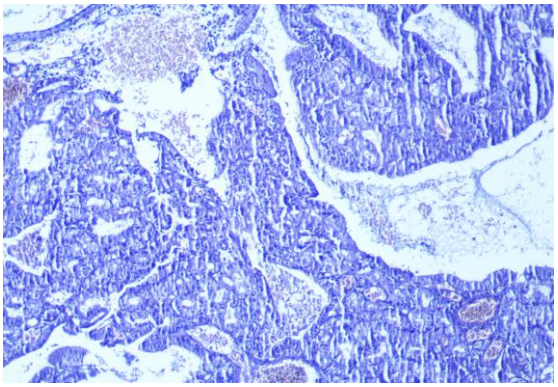

Figure 7. Adenoma, lined by biliary type epithelium with atypia, H&E 200x.

The frequency and pathologic features of acute cholecystitis is unclear. In the present study, acute cholecystitis was found in 8.9% of cases, the percentage is greater than that obtained by Tadashi et al and relatively similar to that obtained by Tyagi SP et al. [34,35]. They were characterized by prominant neutrophilic infiltration ,significant eosinophils with frequent mucosal sloughing, gangrenous changes, and abscess formations which is seen in 4.2% of the cases (figure 1). Furthermore; some cases of xanthogranulomatous mucosal reaction present in acute cholecystitis with congestion and mucosal sloughing.

The frequency of eosinophilic cholecystitis was 4.3% in this study, formed by significant eosinophilic inflammatory cell infiltration exceeding 20 cell/HPF and frequently noticed with xanthogranulo-matous and acute cholecystitis (figure 2). Chronic cholecystitis seen in 464 of the cases 80.6% which form the bulk of the pathologies. 75.9 % is calculous in etiology.

Chronic follicular cholecystitis is seen in 32 cases (5.6%) formed by significant number of reactive lymphoid follicles with active germinal centers in addition to other morphologic features of chronic cholecystitis.(Fig. 3.), the figure is nearly similar to that obtained by Tyagi et al[35] .

The frequency of RAS is not known. RAS is thought to be epithelial herniation due to increased gall bladder inner pressure. They were characterized by a cystic spaces lined by a

layer of columnar epithelium of biliary type in the fibromuscular or subserosal layers (figure 4). In general, RAS is rarely seen in normal gall bladders [36]. RAS is among the lesions of chronic cholecystitis [36]. In the present study, RAS were recognized in 38.7 %. RAS epithelium occasionally showed marked proliferation. The frequency of microliths or inspissated bile within RAS was also unknown. In the present study, they were recognized in (4.2 %) of the cases. Foreign body granulomatous reaction was present around the microliths or inspissated bile in 5 cases. These findings suggest that the microliths or inspissated bile within RAS is frequent in chronic cholecystitis.

The frequency of adenomyomatous change was unclear, but one Indian report showed that it was 8.2% of 415 cholecystectomies [35]. In the present study, they were present in 25.3%. This difference may be due to the difference of the definition of adenomyomatous changes.the present study includes both RAS epithelial change and muscular hypertrophy as a sign for adenomyomatous changes (figure 4).

Metaplastic changes were present in 37.4% of the cases ,include pyloric gland metaplasia 9.2%.Intestinal metaplasia 4.2% and Mucous gland metaplasia 24% of the cases (figure 5). The authors think that the pyloric glands metaplasia emerges from gall bladder stem cells under chronic irritable inflammation[31] .

The frequencyof xanthogranulomatous cholecystitis is reported to be 6.1%, acute cholecystitis cases also contains such pathologic change and this figure is relatively lower than that reported by Dixit et al (8.9%) [37]. It is characterized by diffuse infiltration of foamy macrophages and other mixed acute and chronic inflammatory cells. On macroscopic examination, this entity showed marked thickening of the whole gall bladder, and resembled gall bladder carcinoma (figure 6).Focal xanthogranulomatous changes were frequently associated with mucosal ulcer formation, suggesting that bile in the bladder walls incites the xanthogranulomatous changes [38] .

The incidence of cholesterosis was reported to be 2.7 % in the Indian series [35]. In the present study, it was identified in 5.4%. This difference may be due to variations in fat ingestion. It was characterized by infiltration of foamy macrophages in the mucosa.

Cholesterol polyps which are characterized by a small polyp containing foamy macrophages protruding above the level of mucosa. They were frequently multiple, and grossly small yellow [38,39]. The frequency of gall bladder polyp is reported to be about 4.5 % according to Jorgensen and Jensen [38]. In the present study, the frequency of cholesterol polyp was 2.1 %. It was frequently multiple, and grossly characterized by small yellow polyp.

Gall bladder tubular adenomas were classified into gastric type, intestinal type and biliary type [40]. The frequency of tubular adenoma in the gall bladder was unknown. The present study revealed that the incidence of tubular adenoma is 0.2%. It was single and of biliary type with low grade atypia or low malignant potential.

In the present study, invasive adenocarcinoma was recognized in 9 cases (1.8%). All of these, were tubular and solid glandular non mucinous and non-papillary adenocarcinomas. Invasive and reached muscularis layer except one case invading deeply to the serosal fat. Only two were incidentally found during pathological examination.

It is well known that hepatobiliary cystadenoma and cystadenocarcinoma is predominantly seen in middle-aged female and frequently have ovarian stroma-like mesenchymal stroma [41,42,43] . No mesenchymal stroma was seen in the present study.

In the present study, there were no cases of heterotopic tisues, intraepithelial neoplasms, and other malignancies.

Conclusion

The present data may provide basic knowledge regarding gall bladder pathology including chronic calculous and acute nonspecific cholecystitis with rarity of malignancy and may represent reference for gall bladder lesions at our center as the frequency of gall bladder pathologies varies depending on race, country and institutes.

Recommendations

1) Careful grossing and dissection of gall bladder specimens including fundus,body and

neck sampling as malignancy might be visible only microscopically which needs thorough sampling.

2)Gall bladder epithelial polyp should be categorized histologically according to epithelial histologic type and mention any dysplasia or malignant potential seen in adenomatous polyps.

3) Eosinophilic and follicular cholecystitis needs to diagnosed histologically to provide data for further study of those patients.

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