



HISTOPATHOLOGICAL EXAMINATION OF GALL BLADDER AFTER CHOLECYSTECTOMY : A JUSTIFIED ACT?

Pathology

Dr. Yelda Vyas

Assistant professor, Department of Pathology, NIMS&R, Jaipur

Dr. Madhvi Sanwelka*

Assistant professor, Department of Pathology, NIMS&R, Jaipur *Corresponding Author

ABSTRACT

Introduction Cholelithiasis is a common medical problem throughout the world that frequently leads to surgical intervention. In India, its prevalence ranges from 2 to 29% and more in northern India as compared to southern part of India. It is a multifactorial disease and is more common in females in 4th decade of life, but can also occur in male and children. Incidence of carcinoma gallbladder is found to be only 3% of all gastrointestinal malignancy and mostly found in patients of age more than 50 years. Its 5 year survival rate is only 1-5% as it is diagnosed late. This study is done to find various histopathological changes in gallbladder and to assess the feasibility of performing histopathology on every gall bladder specimen after cholecystectomy. This will enable us to detect discrete carcinomas of gallbladder, which in turn will contribute in reduction morbidity and mortality. **Material and method** This is a prospective study done in National Institute of Medical Science and Research, Jaipur, from January 2022 to January 2023. Total 156 cases were studied. **Result** In the period of 12 months, 156 cholecystectomy specimens were studied. Age of the patients ranged from 8 years to 81 years. Most common age group was 41-50 years. Females were more commonly affected. Female: male ratio was 2.9:1. Most common presenting symptom was abdominal pain (100%), followed by nausea or vomiting (59%) and least was mass in right hypochondrium (3%). Out of total 156 cases, 142 cases (91%) had stone. Most common stone seen was mixed type (47%) followed by cholesterol (43%) and pigment (10%) type. Out of 156 cases, most common was calculus chronic cholecystitis found in 137 cases (88%), followed by chronic acalculus cholecystitis (9%), adenomyomatosis (6%), xanthogranulomatous (3%), acute-on-chronic cholecystitis (1.9%), Cholesterosis (1.2%) and least was eosinophilic cholecystitis and mucosal hyperplasia (0.64% each). One case of parasite and fungus each was also noticed. Out of 156 cases, 152 cases (97%) were benign and only 4 cases (3%) were malignant. Malignancy was common in 5th to 7th decade. All of these 4 malignant cases were found in females and were adenocarcinoma of gallbladder. 3 out of these 4 cases (75%) were moderately differentiated and one (25%) was poorly differentiated adenocarcinoma of gallbladder. **Conclusion** The histopathological spectrum of gallbladder lesions is extremely variable. Most of the gallbladder disease were due to cholelithiasis (stones) and were in females. Incidental diagnosis of malignancy is not rare, we found 4 cases (3%) of malignancy. These cases had no symptoms of malignancy nor any preoperative investigation suggested malignancy. The main strength of this study is that it showed the most comprehensive picture of gallbladder lesions including malignancy, parasite and fungus in our institute. The limitation of this study is that it is a single centre study, short study period and small sample size. We need to conduct more such studies with large sample size to see the exact incidence of malignancies.

KEYWORDS

Gallbladder, Cholecystitis, Cholelithiasis, Carcinoma, Cholecystectomy

INTRODUCTION

Gall bladder is located in foregut and is affected by wide spectrum of pathological diseases, ranging from congenital to inflammatory, malignant or premalignant lesions.¹ It is a pear shaped organ, found at the visceral surface of right lobe of liver.² It is one of the commonest organ resected routinely.³

Histologically, it has three layers namely mucosa, muscularis and serosa. Mucosa is lined by tall columnar epithelium filled with mucus which separates it from bile.^{4,5}

Cholelithiasis is a common medical problem throughout the world that frequently leads to surgical intervention.⁶ In India, its prevalence is ranges from 2 to 29% in general population.⁶ It is more common in northern India as compared to southern part of India.⁶ It is multifactorial disease and is more common in females in 4th decade of life, but can also occur in male and children.⁷ Contributory factors include age, obesity, insulin resistance, genetic susceptibility, alcohol consumption, pregnancy, high cholesterol and drugs.⁷ Calcium, ascorbic acid and fibers in diet has protective effect against cholelithiasis.^{8,9,10}

Bile stasis in gall bladder due to gall bladder dyskinesia is a major cause of gall stones formation. Mucous, calcium and lipids are the three factors which together promotes the nucleation of stones.¹¹ There are three types of stones according to composition-cholesterol, pigment and mixed type of stones.¹² Cholesterol stones are single, yellow and oval in shape, pigment stones are multiple, black and small in size and mixed stones are multiple, variable size and multifaceted.¹³

All these stones irritate epithelium of gall bladder leading to histopathological changes like acute and chronic cholecystitis, metaplasia, dysplasia, pre-malignant and ultimately malignant conditions.^{11,14,15}

As mostly patients are asymptomatic, so carcinoma is often diagnosed late and sometimes incidentally found only on histopathological

specimen. Cholecystectomy performed with clinical diagnosis as of benign lesion based on ultrasonography or computed tomography screening misses significant number of early neoplastic lesions. Selective approach for sending gall bladder specimen leads to missing of premalignant and malignant conditions such as porcelain gallbladder, carcinoma-in-situ.^{16,17} This selective approach is justified by claiming that it reduces workload of pathologist and also reduces financial burden of patient.

Incidence of carcinoma gallbladder is found to be only 3% of all gastrointestinal malignancy and mostly found in patients of age more than 50 years of age. Its 5 year survival rate is only 1-5% as it is diagnosed late. Mostly it is adenocarcinoma but can be adenosquamous, squamous and other rare type.¹⁸

This study is done to find various histological changes in gallbladder and to assess the feasibility of performing histopathology on every gall bladder specimen, so to pick discrete carcinoma of gallbladder, which in turn will reduce the mortality rate.

MATERIAL AND METHOD

This study is a prospective study done in National Institute of Medical Science and Research, Jaipur, from February 2020 to January 2021. Total 156 cases were studied. Inadequate, autolysed samples and specimens without complete medical records were not included in this study. Patients history was obtained through medical records and requisition forms. The specimens were collected in 10% formalin and kept for fixation for 24 hours. Sections were taken from fundus, body and neck of the gallbladder. All the gross morphological details and type of stone, if present were noted. Additional sections from abnormal mucosa were taken. These sections then stained with Hematoxylin and Eosin stain and stained slides were observed under microscope. Details were entered into Microsoft excel sheet and analysed.

RESULT

In the period of 12 months, 156 cholecystectomy specimens were studied. Age of the patients ranged from 8 years to 81 years. Most

common age group was 41-50 years (table 1). Females were more commonly affected. Female: male ratio was 2.9:1 (table 2). Most common presenting symptom was abdominal pain (100%), followed by nausea or vomiting (59%) and least was mass in right hypochondrium (3%) as shown in table 3. Out of total 156 cases, 142 cases (91%) had stone. Most common stone seen was mixed type (47%) followed by cholesterol (43%) and pigment (10%) type (table 4).

Table 1- Distribution of cases according to age N=156)

Age (years)	No of patients	Percentage (%)
1-10	1	1
11-20	3	2
21-30	18	11
31-40	28	18
41-50	40	26
51-60	35	22
61-70	25	16
71-80	5	3
81-90	1	1
Total	156	100

Table 2:- Distribution of cases according to gender (n=156)

Gender	Number of cases	Percentage
Male	40	26
Female	116	74
Total	156	100

Table 3:- Presenting symptoms (n=156)

Symptoms	Number of cases	Percentage (%)
Abdominal pain	156	100
Nausea and/or vomiting	92	59
Mass in right hypochondrium	4	3

Table 4:- Gender wise distribution of types of stones (n= 142)

Type of stone	Mal	%	Female	%	Total	%
Mixed	11	31	55	51	66	47
Pigment	10	29	5	5	15	10
Cholesterol	14	40	47	44	61	43
Total	35	100	107	100	142	100

Table 5:- Histopathological report (n=156)

Lesion	Number of cases	Percentage
Chronic calculus cholecystitis	137	88
Acute on chronic cholecystitis	3	1.9
Chronic acalculus cholecystitis	14	9
Eosinophilic cholecystitis	1	0.64
Xanthogranulomatous cholecystitis	5	3
Adenomyomatosis	10	6
Cholesterosis	2	1.2
Mucosal hyperplasia	1	0.64
Adenocarcinoma	4	2.5
Parasite	1	0.64
Fungus	1	0.64

Table 6:- Age wise distribution of benign and malignant lesion

Age (years)	Benign	Malignant
11-30	22	0
31-50	66	1
51-70	57	3
71-90	6	0
Total	152	4

Table 7:- Incidence of benign and malignant lesions

Gender	Benign	%	Malignant	%
Male (40)	40	100	0	0
Female (n=116)	112	97	4	3
Total	152		4	

Out of 156 cases, in benign cases most common was calculus chronic cholecystitis found in 137 cases (88%), followed by chronic acalculus cholecystitis (9%), adenomyomatosis (6%), xanthogranulomatous (3%), acute-on-chronic cholecystitis (1.9%), Cholesterosis (1.2%) and least was eosinophilic cholecystitis and mucosal hyperplasia (0.64% each).

One case of parasite and fungus each was also noticed (Table 5/Figure 1a and 1b)

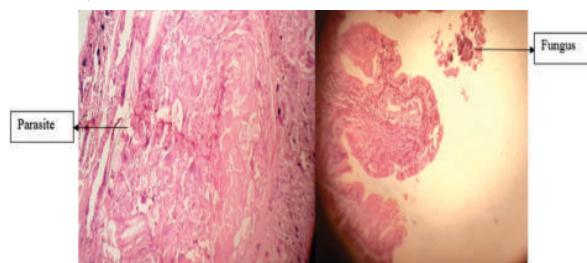


Figure 1: (a) Photomicrograph of gallbladder showing parasite in the muscularis layer.(H& E X400). (b) Photomicrograph of gallbladder showing fungus is seen. (H & E X400)

Out of 156 cases, 152 cases (97%) were benign and only 4 cases (3%) were malignant. Malignancy was common in 5th to 7th decade (Table 6). All of these 4 malignant cases were found in females and were adenocarcinoma of gallbladder (Table 7). 3 out of these 4 cases (75%) were moderately differentiated adenocarcinoma and one (25%) was poorly differentiated adenocarcinoma of gallbladder. (Figure 2a and 2b)

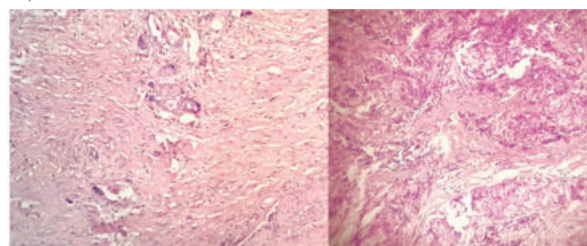


Figure 2: (a) Photomicrograph of gall bladder showing moderately differentiated adenocarcinoma. (H & E X400). (b) Photomicrograph of gallbladder showing poorly differentiated adenocarcinoma . (H & E X400).

DISCUSSION

Cholelithiasis is a common world wide illness which needs cholecystectomy. There is a long list of lesions associated with gallbladder, it can be inflammatory namely cholecystitis, cholesterosis, xanthogranulomatous, adenomyomatosis, parasites and fungus or premalignant like hyperplasia, metaplasia, dysplasia or malignant. All these cases are not diagnosed on ultrasonography. Hence, all gallbladder should be sent for histopathological assessment.¹⁴

In the present study, patient ranged between 8-81 years. Most of them were in 4th to 6th decade of life. Majority of them were females. Female : male ratio is 2.9:1. Similar findings are seen in studies done by Sumit et al¹⁹, MR et al²⁰, Banerjee et al²¹, Siddiqui et al²², Channa et al²³, Murshid et al²⁴. The high incidence of gall bladder disease in females is due to their sedentary lifestyle and presence of female sex hormone which leads to development of gallstones.

All patients presented with pain in abdomen which is consistent with study done by Laghari et al²⁵ but slightly different from Siddiqui et al²² which showed 90% patients had pain abdomen.

In our study 142/156 (91%) cases had multiple stones in their gallbladder. This is in concordance with studies done by Dattal DS et al²⁶, Goyal S et al²⁷, Khanna et al²⁸, Gupta K et al²⁹ which showed 91.8%, 69.64%, 85%, 88.02% multiple stones respectively. Thus all studies indicates that clinical symptoms are more in cases who had stones.

We found that most common stone seen was of mixed type (47%) followed by cholesterol (43%) and pigment (10%) type. This finding is similar to studies done by Mathur SK et al¹⁴, Goyal S et al²⁷, Gupta K et al²⁹, Baig SJ et al³⁰.

On histopathological examination, chronic cholecystitis is most common finding in our study (96%), which is similar to studies of Baig SJ et al³⁰, Tyagi et al³¹, Gupta K et al²⁹, Menon et al³², Siddiqui et al²², Stanchu et al³³ showed 60%, 50.8%, 53.22%, 64.8%, 92.3% and 88.9% cases respectively.

Cholesterosis was seen in 1.2% of cases which is less than other studies done by Giri S et al¹⁹, Gupta K et al²⁰ and Kumbhakar et al³⁴ which showed 7.61%, 7.14%, 7.50% cases respectively.

Only 1(0.64%) case of hyperplasia was found which is comparable to the studies done by Singh P et al³⁵ (2.5%) and Elfing et al³⁶. Elfing et al³⁶ stated that hyperplasia occurs due to chronic irritation of mucosa by calculi.

6% of cases had adenomyomatosis which is comparable to studies of Gupta K et al²⁹ (3%) and Terada et al³⁷ (3.68%). We found 1 case (0.64%) of eosinophilic cholecystitis which is similar to Gupta et al²⁹, Kaur et al³⁸ who found 0.69% and 0.78% cases respectively.

Xanthogranulomatous cholecystitis was found in 3% of cases which is comparable to Gupta K et al²⁹, Shah et al³⁹ and Vahini et al⁴⁰ which showed 2.07%, 2% and 1.81% cases respectively.

In our study we found 4 cases (2.5%) of adenocarcinoma. This is similar to studies done by Siddiqui et al²², Gupta K et al²⁹, Shah et al³⁹, Selvi et al¹³, Mohan et al⁴¹, Pradhan et al⁴² and Kaur et al³⁸ which showed 2.7%, 1.15%, 2%, 1.20%, 1.09%, 1.05% and 0.78% cases respectively. Study done by Vahini et al⁴⁰ showed 4.5% cases of carcinoma. All cases in our study were presented with long history of pain in abdomen and of chronic cholecystitis. Female sex hormone is the main etiological factor for the development of malignancy. So early menarche, multiple pregnancy, early pregnancy and delay menopause increases the risk.

The issue of doing histopathology on every specimen of gallbladder is justified because premalignant and malignant lesions are only found by microscopic examinations when there are no clinical symptoms in patients suggestive of malignancy and these cases can be missed on radiological investigations.

Grading of adenocarcinoma was found moderately differentiated to poorly differentiated. No case of squamous cell carcinoma or other variant of malignancy was found on histopathology.

CONCLUSION

The histopathological spectrum of gallbladder lesions is extremely variable. Most of the gallbladder disease were due to cholelithiasis (stones) and were in females. Incidental diagnosis of malignancy is not rare, we found 4 cases (2.5%) of malignancy. These cases had no symptoms of malignancy nor any preoperative investigation suggested malignancy. Old patients and long duration of symptoms are more prone for malignancy. We therefore, strongly advocate routine histopathological investigation of all Cholecystectomy specimens to ensure reduction in mortality rate of patients.

The main strength of this study is that it showed the most comprehensive picture of gallbladder lesions including malignancy, parasite and fungus in our institute. The limitation of this study is that it is a single center study, short study period and small sample size. We need to conduct more such studies with large sample size to see the exact incidence of malignancies.

Funding

None as stated by authors

Conflict of interest

None as stated by authors

REFERENCES

- Hansel DE, Maitra A, Argani P. Pathology of the gallbladder: a concise review. *Current Diagnostic Pathology*. 2004; 10(4):304-17.
- Standring S, Borley NR, Collins P, Crossman AR, Gatzoulis MA. The anatomical basis of clinical practice. *Gray's anatomy*. Edinburgh: Churchill Livingstone, 2008
- Lack EE. Pathology of the pancreas, gallbladder, extrahepatic biliary tract, and ampullary region. Oxford University Press, 2003, 20.
- Kuwer R, Klinkspoor JH, Osborne WR, Lee SP. Mucous granule exocytosis and CFTR expression in gallbladder epithelium. *Glycobiology*. 2000; 10(2):149-57.
- Mani H, Climent F, Colombo L, Pittaluga S, Raffeld M, Jaffe ES. Gall bladder and extrahepatic bile duct lymphomas: clinicopathological observations and biological implications. *The American journal of surgical pathology*. 2010; 34(9):1277.
- Singh P, Jaiswal VK, Verma N, Rath M, Sharma B, saroj AK. Histopathological spectrum of gall bladder lesion and association with cholelithiasis. *IJMHR*. 2018; 4(9): 134-138.
- Randi G, Franceschi S, La Vecchia C. Gallbladder cancer worldwide: geographical distribution and risk factors. *International journal of cancer*. 2006; 118(7):1591-602.
- Cuevas A, Miquel JF, Reyes MS, Zanlungo S, Nervi F. Diet as a risk factor for cholesterol gallstone disease. *Journal of the American College of Nutrition*. 2004; 23(3):187-96.
- Tsai CJ, Leitzmann MF, Willett WC, Giovannucci EL. The effect of long-term intake of cis unsaturated fats on the risk for gallstone disease in men: a prospective cohort study. *Annals of internal medicine*. 2004; 141(7):514-22.
- Leitzmann MF, Tsai CJ, Stampfer MJ, Rimm EB, Colditz GA, Willett WC, Giovannucci EL. Alcohol consumption in relation to risk of cholecystectomy in women. *The American journal of clinical nutrition*. 2003; 78(2):339-47.
- Zaki M, Al-Refeidi A. Histological changes in the Human Gallbladder Epithelium associated with gallstones. *Oman Medical Journal*, 2009, 24(4).
- Conte D, Fraquelli M, Giunta M, Conti CB. Gallstones and liver disease: an overview. *J Gastrointestinal Liver Dis*. 2011; 20(1):9-11.
- Selvi TR, Sinha P, Subramaniam PM, Konapur PG, Prabha CV. A clinicopathological study of cholecystitis with special reference to analysis of cholelithiasis. *International journal of basic medical science*. 2011; 4:68-72.
- Mathur SK, Duhan A, Singh S, Aggarwal M, Aggarwal G, Sen R *et al*. Correlation of gallstone characteristics with mucosal changes in gall bladder. *Tropical gastroenterology*. 2012; 33(1):39-44.
- Zuhair M. Histological Changes of Gall Bladder Mucosa: Correlation with Various Types of Cholelithiasis. *Iraqi journal of community medicine*. 2011; 24(3):234-40.
- Underwood JCE: A recovery plan for histopathology. *Royal Coll Path Bulletin* 2001, 113:12-14.
- Wilkinson DS: Carcinoma of the gall bladder: an experience and review of the literature. *Aust NZ J Surg* 1995, 65:724-727.
- Dowling GP, Kelly JK. The histogenesis of adenocarcinoma of the gallbladder. *Cancer*. 1986; 58(8):1702-8.
- Giri S. Histopathological changes in gallbladder mucosa associated with cholelithiasis. *International Journal of Current Research and Review*. 2013; 5(4):126.
- Khan MR, Raza SA, Ahmad Z, Naem S, Pervez S, Siddiqui AA *et al*. Gallbladder intestinal metaplasia in Pakistani patients with gallstones. *International Journal of Surgery*. 2011; 9(6):482-5.
- Banerjee A, Tapadar A. Spectrum of histopathological changes in cholecystitis. *Int. J Biol Med Res*. 2015; 6(1):4769-74.
- Siddiqui et al.: Routine histopathology of gallbladder after elective cholecystectomy for gallstones: waste of resources or a justified act? *BMC Surgery* 2013 13:26.
- Channa NA, Soomro AM, Ghangro AB: Cholecystectomy is becoming an increasingly common operation in Hyderabad and adjoining areas. *Rawal Med J* 2007, 32(2):128-130.
- Murshid KR: Symptomatic gallstones: a disease of young Saudi women. *Saudi J Gastroenterol* 1998, 4(3):159-162.
- Laghari AA, Talpur KAH, Malik AM, Khan SA, Memon AI: Laparoscopic Cholecystectomy in complicated gallstone disease. *J Liaquat Uni Med Health Sci* 2008, 7(1):18-24.
- Dattal DS, Kaushik R, Gulati A, Sharma VK. Morphological spectrum of gall bladder lesions and their correlation with cholelithiasis. *International Journal of Research in Medical Sciences*. 2017; 5(3):840-6.
- Goyal S, Singla S, Duhan A. Correlation between gallstones characteristics and gallbladder mucosal changes: A retrospective study of 313 patients. *Clinical Cancer Investigation Journal*. 2014; 3(2):157.
- Khanna R, Chansuria R, Kumar M, Shukla HS. Histological changes in gallbladder due to stone disease. *Indian J surg*. 2006; 68(4):201-4.
- Gupta K, Faiz A, Thakral RK, Mohan A, Sharma VK. The spectrum of histopathological lesions in gallbladder in Cholecystectomy specimens: *Int J Clin Diagnol Pathol*:2019;2(1):146-151.
- Baig SJ, Biswas S, Das S, Basu K, Chattopadhyay G. Histopathological changes in gallbladder mucosa in cholelithiasis: correlation with chemical composition of gallstones. *Tropical gastroenterology: official journal of the Digestive Diseases Foundation*. 2002; 23(1):25-7.
- Tyagi SP, Tyagi N, Maheshwari V, Ashraf SM, Sahoo P. Morphological changes in diseased gall bladder: a study of 415 cholecystectomies at Aligarh. *Journal of the Indian Medical Association*. 1992; 90(7): 178-81.
- Memon W, Khanzada TW, Samad A, Kumar B: Histopathology sepectrum of gallbladder specimens after cholecystectomy. *Pak J Med Sci* 2011, 27(3):533-536.
- Stanchu M, Caruntu I, Giusa S, Dobrescu G. Hyperplasia, Metaplasia, dysplasia and neoplasia lesions in chronic cholecystitis - a morphological study *Rommonian J Morphol Embryol*. 2007; 48(4):335-42.
- Kumbhakar D. a histopathological study of Cholecystectomy specimen. *JMSCR*:2016; 4(7): 11234-11238.
- Singh P, Jaiswal VK, Verma N, Rath M. histopathological spectrum of gallbladder lesions and association with Cholelithiasis. *Int jour Med and Res*:2018;4(9):134-138.
- Elfving G, Teie H, Deger H, Makalla T. Mucosal hyperplasia in the gallbladder demonstrated by plastic models. *Acta Pathol Microbiol Scand*. 1969; 77:384-8.
- Terada T. Histopathologic features and frequency of gall bladder lesions in consecutive 540 cholecystectomies. *International journal of clinical and experimental pathology*. 2013; 6(1):91.
- Kaur A, Dubey VK, Mehta KS. Gallbladder mucosal changes associated with chronic cholecystitis and their relationship with carcinoma gallbladder. *JK Science*. 2012; 14(2):89.
- Shah H, Khan MA, Shah W. Histopathological pattern of 400 cholecystectomy specimens. *Journal of Postgraduate Medical Institute (Peshawar-Pakistan)*. 2016, 30(3).
- Vahini G, Premalatha P, Mathi A, Krishna R, Renuka IV. A clinicopathological study of gallbladder lesions. *IOSR-JDMS*. 2015; 14(2):15-20.
- Mohan H, Punia RP, Dhawan SB, Ahal S, Sekhon MS. Morphological spectrum of gallstone disease in 1100 cholecystectomies in North India. *Indian Journal of Surgery*, 2005, 67(3).
- Pradhan SB, Joshi MR, Vaidya A. Prevalence of different types of gallstone in the patients with cholelithiasis at Kathmandu Medical College, Nepal. *Kathmandu University Medical Journal*. 2009; 7(3):268-71.