

Research Article

Incidental carcinoma of gallbladder in north India: is routine histopathology of all cholecystectomy specimens justified?

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ABSTRACT

Background: Gallstones can cause varied spectrum of histopathology. Xanthogranulomatous cholecystitis and metaplasia have been shown to have association with carcinoma gallbladder. Incidental carcinoma of the gallbladder is a nightmare for the patient. Routine histopathology of all cholecystectomy specimens is an effective policy for its early diagnosis and management.

Methods: It is a retrospective study of histopathology of cholecystectomy specimens related to gallstones disease done at a rural government in north India. All patients with preoperative or intraoperative gross malignancy of gallbladder were excluded from study.

Results: In our study, females were predominating over males with a ratio of 6.07:1. The mean of all patients was 44.16±14.64 years. Chronic cholecystitis was most common (69.81%) histopathological entity. Incidental carcinoma was also revealed in 1.9 % of the cases. Metaplasia and xanthogranulomatous cholecystitis was reported in about 6% cases. Mixed stones were most common type reported in 76.79% cases. Multiple stones (72.8%) were more common than single stones. Majority (58%) of the cases in our study were operated by laparoscopic technique. Gallbladder perforation was most common complication noticed in about 4.15% cases.

Conclusions: Despite meticulous preoperative investigations and gross specimen examination, incidental carcinoma of gallbladder is a rule rather than exception in significant number of cases. A routine histopathology of specimen should be considered especially in high risk zones of carcinoma gallbladder.

Keywords: Carcinoma, Cholecystectomy, Cholelithiasis, Gallstone

INTRODUCTION

Cholecystectomy is commonly performed procedure all over the world. It is being done for a wide spectrum of diseases ranging from benign to neoplastic conditions. It is significant health problem affecting 10-15 % of adult population in western world.¹ Cholelithiasis is most common indication of cholecystectomy in north India with prevalence rates varying from 2-29 %.^{2,3} It is seven

times more common in north India than south with female to male ratio of 3.1:1.^{4,5} It can lead to chronic cholecystitis, acute cholecystitis, emphysema, mucocoele, gangrene of gallbladder, carcinoma and gallbladder perforation. Histopathological analysis may reveal myriad of disorders including chronic cholecystitis, acute cholecystitis, cholesterosis, xanthogranulomatous cholecystitis, adenomatous hyperplasia, follicular cholecystitis, metaplasia and carcinoma of gallbladder.

Carcinoma of gallbladder is most common malignancy of biliary tract.⁶ It is an aggressive disease with a dismal prognosis. Incidental carcinoma has been reported in 0.3-1.5% of cholecystectomies done for cholelithiasis.^{6,7} North India is in high risk zone of gallbladder carcinoma with an annual incidence rate of 21.5/1,00,000.¹ Patients of gallstones are prone for carcinoma with a relative risk of 4.9.¹ Whether routine histopathology of all cholecystectomy specimens should be done or not is a matter of debate. Rarity of incidental gallbladder carcinoma along with high load of cholecystectomy specimens demands a selective approach for histopathological analysis to improve its cost effectiveness. However, aggressive nature of tumor along with unfortunate diagnostic misses in early stage demands routine analysis especially in high risk zones of gallbladder carcinoma.

The aim of our study is to assess histopathological spectrum of all cholecystectomy specimens in rural population of north India with a special focus on current trends of incidental gallbladder carcinoma in this defined high risk zone of world.

METHODS

It is a retrospective study 530 patients undergoing cholecystectomy for gallstones from June 2012 to June 2015 in our surgical unit at BPS GMCW Khanpur kalan India. The hospital records of these patients were reviewed. A detailed clinical history and thorough physical examination was done in all cases. Routine ultrasonography and blood investigations were done. Both open and laparoscopic techniques were used in surgery. Only ultrasonographically documented thick walled cholecystectomy specimens were grossly examined after removal on table. All specimens were routinely sent for histopathological analysis.

Exclusion criteria

All cases with gross malignancy of gallbladder diagnosed preoperatively or intraoperatively were excluded from study.

The data was analysed with SPSS 20.0 version. Statistical analysis was performed by using analysis of variance for averages and Chi-square test for contingency tables and proportions.

RESULTS

Table 1: Age distribution of cases.

Age group	No. of patients	% of cases
11-20	14	2.64
21-30	112	21.13
31-40	126	23.77
41-50	112	21.13
51-60	98	18.49
61-70	56	10.57
71-80	10	1.89
>80	2	0.38

Cholelithiasis is characteristically prevalent in 'fatty, fertile females of forties'. In our study, it was most common in fourth decade of life as depicted in table 1. About two third of the cases were present in 20-50 years of age group. The mean age of patients with gallstones was 44.16 years with a standard deviation of 14.64 years. Both the youngest (14 years) and oldest (90 years) patient was a female. Out of total 530 cases, 455 were females while 75 were males. The female to male ratio was 6.07:1 showing a female preponderance as depicted in table 2.

Although all histopathological conditions showed a female predominance but cholesterolosis, follicular cholecystitis and metaplasia were significantly common in females. The mean age of adenomatous hyperplasia, carcinoma, follicular cholecystitis and xanthogranulomatous cholecystitis was significantly higher than rest of the cases. Chronic cholecystitis was the most common variety followed by acute cholecystitis, cholesterolosis, metaplasia, xanthogranulomatous cholecystitis and carcinoma.

Table 2: Histopathological diagnosis of cases with mean age and sex distribution.

Histopathology	Females	Males	Total	% of total	Mean age $\pm$ SD
Acute cholecystitis	41	21	62	11.70	42.74 $\pm$ 14.37
Chronic cholecystitis	324	46	370	69.81	44.31 $\pm$ 14.56
Follicular cholecystitis	04	00	04	0.75	53.50 $\pm$ 13.27
Xanthogranulomatous cholecystitis	12	02	14	02.64	51.85 $\pm$ 13.21
Adenomatous hyperplasia	02	00	02	0.38	58.00 $\pm$ 2.82
Metaplasia	18	00	18	03.40	42.22 $\pm$ 15.57
Cholesterolosis	46	04	50	09.43	40.08 $\pm$ 12.48
Carcinoma	08	02	10	01.90	53.60 $\pm$ 22.75
Total	455	75	530	100	44.16 $\pm$ 14.64

Majority of the cases (79.45 %) of chronic cholecystitis in our study were having mixed type of stones as illustrated in table 3. A statistically significant association ($p=0.03$) was found between chronic cholecystitis and multiple mixed stones. Carcinoma of gallbladder was also predominantly associated with multiple mixed stones. Cholesterol stones were present in only 20 % cases of cholesterolosis while 72 % cases had mixed stones. Xanthogranulomatous cholecystitis was also predominantly associated with multiple mixed stones.

Laparoscopic cholecystectomy is 'gold standard' procedure for management of gallstones all over the world. Majority (58 %) of the cases in our study were also operated by this technique as illustrated in figure 1.

However minilap (27 %) and open (15%) methods were used in rest of the cases. Gallbladder perforation was most common complication noticed in about 4.15 % of the cases. A haemorrhagic drain output (up to 300 ml) was also reported in 17 cases. All cases were managed conservatively with sub hepatic drain. Postoperative bile leak was reported in 13 cases varying from 30 -500 ml/day, with longest duration of 8 days. All of them were successfully managed with drains. Idiopathic liver injuries were reported in 11 cases, all of them were of grade 1. These injuries were indulged either during epigastric port placement or during gallbladder dissection which were managed conservatively with abgel and electro cautery. Wound infection was also reported in 10 cases.

Table 3: Distribution of cases according to no. and type of stones.

Histopathology	Cholesterol stones	Mixed stones	No stones	Pigment stones	Single stones	Multiple stones
Acute cholecystitis	15	41	4	2	14	44
Adenomat.hyperplasia	0	2	0	0	2	0
Carcinoma	4	6	0	0	4	6
Chronic cholecystitis	38	294	14	26	84	272
Cholesterolosis	10	36	4	0	32	14
Follicular cholecystitis	0	4	0	0	0	4
Metaplasia	0	16	2	0	2	14
Xanthogranulomatous cholecystitis	2	12	0	0	6	8

DISCUSSION

Cholelithiasis can cause histopathological changes in gall bladder mucosa varying from acute cholecystitis, chronic cholecystitis, follicular cholecystitis, xanthogranulomatous cholecystitis, cholesterolosis, adenomatous hyperplasia, metaplasia and carcinoma. Genetic susceptibility for gallstone formation have been studied with a relative risk of 5 times in relatives of gallstone patients.^{1,8} Geography and ethnicity also plays an important role in the prevalence of gall stones. North American Indian natives, Mabuchi Indians and Mexican Americans have highest reported incidence of gall stones varying from 49.4% to 64.1%^{9,10} Asian population have intermediate prevalence ratio¹¹

The incidence of gallstones increases markedly after 40 years, reaching up to 4 to 10 times in old age.^{12,13} In our study mean age of presentation was 44.16±14.64 years. In Coelho et al study the mean age was 60.2 years.¹⁴ While Bawaheb et al in 2013 reported a mean age of 41.3±14.7 years.¹⁵ Tyagi SP et al also reported a mean age of 43.6 years in their study of 415 cases.¹⁶

In the present study females were predominating over males with a ratio of 6.07:7. Similar results were also

reported by various studies from this region.^{2,5,6} In present study, disease has almost a uniform incidence in 20-50 years age group with a slight peak in 4th decade. Kafle et al and Mathur et.al also reported the analogous results in their studies.^{17,18}

Chronic cholecystitis was the most common presentation (69.81%) of the gallstones with a mean age of 44.31±14.56 years. A statistically significant association ($p=0.03$) was found between chronic cholecystitis and multiple mixed stones (chi square test). Majority (79.45%) of these cases had multiple mixed stones. Meman et al and Tyagi et al reported 64.8% and 50.8% cases of chronic cholecystitis in their studies respectively.¹⁹ Mathur et al could not found a significant association between chronic cholecystitis and type of stones. Juvomen et al reported a high histopathology incidence of between type of stones and mucosal changes in gall bladder in their study.²¹

Cholesterolosis is characterized by mucosal villous hypertrophy and deposition of cholesterol esters in epithelial macrophages. It is usually clinically asymptomatic and incidentally diagnosed on histopathology. It was reported in 9.43% cases in present study. Akin results were also reported by Rao et al

(13.4%) and Mathur et al (6%) in their studies respectively. It was predominantly seen in female patients (92%) in our study. Rao et al also reported female

predominance in their study. Majority (72%) of these cases have mixed stones. It has a strong negative correlation with carcinoma gallbladder.

Table 4: Complications of cholecystitis.

No.	Complication	Males	Females	Total	% age
1	Gallbladder perforation	08	14	22	04.15
2	hemorrhage	05	12	17	03.20
3	Bile leak	05	08	13	02.45
4	Liver injury	03	08	11	02.08
5	Wound infection	02	08	10	01.89
6	Scar sinus	01	04	05	0.94

Xanthogranulomatous cholecystitis (XGC) is not an uncommon entity and is frequently misdiagnosed as carcinoma of gallbladder. It was detected in 2.64% cases in present study. Majority (85%) of them were females with a mean age of 51.85 ± 13.21 years. It has been reported to have increased association with carcinoma gallbladder varying from 0.2-15% in recent studies.²²⁻²⁴ Hale et al in their meta analytical study of 1599 cases in 2014 have reported xanthogranulomatous cholecystitis in 1.3-1.9% cases except India (8.8%).²² They also reported its association with carcinoma gallbladder varying from 3.3 % in European population to 5.1-5.9% in rest of the world. Majority of these cases were associated with gallstones. Indian literature also reported an incidence of 3-3.2%.

Metaplasia of gallbladder is an early histopathological change in metaplasia-dysplasia-carcinoma cascade. It was reported in 3.40% cases in our study with a mean age of 42.22 ± 15.57 years. All of them were females with predominance of mixed variety of stones. Intestinal metaplasia was most common type followed by gastric and squamous metaplasia. It was more commonly associated with multiple stones (66.67%) than single ones. Mathur et al and Yaylak et al have reported a higher incidence of metaplasia (18% and 7.9% of cases respectively) in their studies while Mittal et al have reported a low incidence (0.8%) in their study.

Incidental carcinoma of gallbladder is not an uncommon entity. Nonspecific clinical presentation and diagnostic challenge in early stage for radiologists encompasses difficulty in its preoperative diagnosis. Stage of carcinoma at presentation plays a critical role in prognosis of disease. Despite availabilities of newer diagnostic tools and careful macroscopic examination, a significantly large proportion of these cases are still missed even at tertiary care centres.²⁵⁻²⁷ It was revealed in 1.9 % cases in our study. Majority of them (80%) were females with a mean age of 53.60 ± 22.75 years. The youngest patient was 30 years of age while oldest one was of 90 years. In our study also, 60% of the cases were

below the age of 45 years. Mittal et al in their retrospective study of 1312 cases also reported 1 % cases of incidental gallbladder carcinoma with a female predominance (84%). Mean age of these patients (56.2 years) was comparable with our study. Pradhan et al also reported the incidental carcinoma in 2.63 % cases with female dominance (4:1).²⁸ Mathur et al also reported incidental carcinoma in 2% cases. All of them were females with a mean age of 61 years. Mean age of carcinoma was higher than benign gallstones consistently in all these studies.

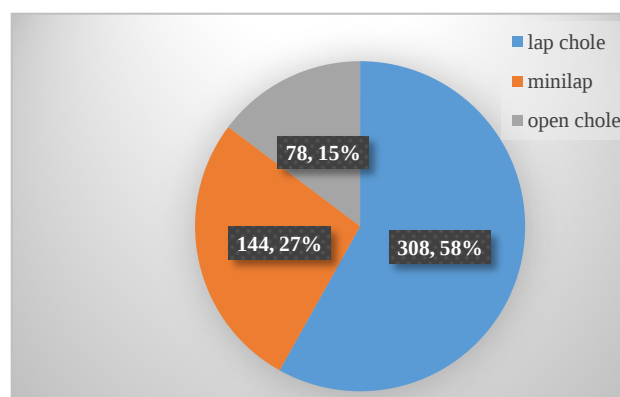


Figure 1: Operative techniques used for cholecystectomy.

Literature is biased on need of routine histopathology of all gallstones related cholecystectomy specimens. Recently few studies have refuted its usefulness in all cases stating that it not only overburdening our pathologists but also cost ineffective due to low incidence of incidental gallbladder carcinoma.²⁹⁻³² Routine histopathological examination of all gallstones related cholecystectomy specimens is a safety link for earliest detection of this carcinoma. High index of suspicion is warranted specially in high risk regions of carcinoma gallbladder like north India for better prognosis. A high burden of disease even at a significantly young age is an alarming sign in our region. It has been a standard

practice over the decades to assess all specimens histopathologically to rule out carcinoma. Moreover, recent studies at apex institutes also strongly justified this recommendation.^{6,33} The royal college of pathologists have also recommended routine histopathological analysis of all specimens of gallstones related cholecystectomies.³⁴

It has been reported by various studies that majority of the cases of gallbladder carcinoma are suspected by either during ultrasonography or on gross examination of the specimen and hence only these suspected cases should be sent for histopathology.^{5,31,32} On the contrary, other studies have doubted their claim with evidence of a significant number of missed incidental carcinoma cases in their studies despite standard investigations and specimen examination.^{6,25-27} In present study also we missed all 10 cases of incidental carcinoma although our selective approach of specimens examination only in thick walled gallbladder was also responsible for this lapse. Therefore cases of missed incidental carcinoma cannot be justified by increased cost and pathologist's workload and a routine histopathology of all cholecystectomy specimens should be advised beyond doubt.

CONCLUSION

Gallstones disease can have a variegated spectrum on histopathology. In high risk zones of carcinoma gallbladder like north India, cases of xanthogranulomatous cholecystitis and metaplasia need careful assessment to rule out associated carcinoma. Incidental gallbladder carcinoma is a nightmare for patients after cholecystectomy. Despite careful preoperative investigations and meticulous gross examination, a significant no. of incidental carcinoma cases are still missed. Although a selective approach of histopathology can decrease cost and burden on pathologist to a large extent but it will also result in missing early staged carcinoma and hence preventable mortality if timely offered curative treatment. Therefore a routine histopathology of all cholecystectomy specimens should be considered in all cases especially in high risk zones of carcinoma gallbladder as a token of respect to human life.

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