

## FREQUENCY OF GALL BLADDER CARCINOMA IN CHOLECYSTECTOMY SPECIMENS- A REVIEW OF 5 YEARS IN UNIVERSITY HOSPITAL IN PUNJAB

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### **Introduction**

Gall Bladder disease is a very common problem worldwide. According to recent data of the national registry program of India, northern part of India especially the gangetic belt has the highest incidence.<sup>1</sup>The incidence of gall stone disease has increased in Asian countries owing to change in their food habits, as diet in asian countries are high in calories and fat.<sup>2</sup>

Various epidemiological reviews have reported that GB Cancer is rare in India, with incidence rates of 0.5 and 1.3/100000 population in men and women, respectively, reported from Mumbai in Western India; however, the incidence rates are as high as 9/100,000 in northern part of India.<sup>2</sup> In Delhi, GBC (incidence rate 6.6/100,000) is the fourth most common cancer (following cervix, breast and ovary) and the most common gastrointestinal cancer in women (more common than esophagus, stomach, and colon). In Jammu, GBC is reported as the third most common cancer (after cervix and breast) in women.<sup>3</sup> GBC is prevalent in other countries in the northern part of the Indian subcontinent including Pakistan and Bangladesh.<sup>4</sup>

Incidental gallbladder carcinoma (IGBC) is defined as cancer discovered at the time of histopathological examination of the specimen after cholecystectomy done for benign gallbladder disease without clinico-radiological and intraoperative suspicion of malignancy.<sup>5,6</sup> Studies have shown that the incidence of IGBC ranges from 0.2% to 3.3% in all cholecystectomies specimen of benign disease. The definitive treatment of symptomatic gallstone disease is a laparoscopic or open cholecystectomy as per the demand of clinical situation and preference of the patient. Keeping in view the incidence of IGBC, every cholecystectomy specimen should be sent for histopathological examination to increase the detection rate of occult early-stage IGBC in benign gallbladder diseases.<sup>7</sup>

Approximately 90% of Gall Bladder cancer have accompanying stone, but only 2% to 3% of patients with cholelithiasis will develop Gall Bladder carcinoma.<sup>8</sup>Despite of improved imaging techniques preoperative diagnosis of Gall Bladder carcinoma is not always possible, 80% of cases present in late stages.<sup>9</sup>

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 of 649 patients undergoing cholecystectomy for gallstones from Jan 2015 to Dec 2019 in our surgical unit at GGS Medical college, Faridkot Punjab 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. All specimens were 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 statistically. 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 the cases**

| Age group    | Number of patients | Percentage of cases |
|--------------|--------------------|---------------------|
| 11-20        | 2                  | 0.31%               |
| 21-20        | 46                 | 7.18%               |
| 31-40        | 173                | 27%                 |
| 41-50        | 211                | 32.96%              |
| 51-60        | 120                | 18.75%              |
| 61-70        | 76                 | 11.8%               |
| 71-80        | 12                 | 1.8%                |
| <b>TOTAL</b> | <b>640</b>         |                     |

Cholelithiasis is characteristically prevalent in 'fatty, fertile females of forties'. In our study, total of 640 cholecystectomy was done during this period. It was most common in fourth decade of life as depicted in table 1 (32.96%). About two third of the cases were present in 30-60 years of age group. There were 578 females and 62 males.

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

| Histopathology                    | Females | Males | Total | % of total |
|-----------------------------------|---------|-------|-------|------------|
| Acute cholecystitis               | 41      | 11    | 52    | 8.1%       |
| Chronic cholecystitis             | 463     | 46    | 509   | 79.53%     |
| Acute on chronic cholecystitis    | 6       | 0     | 6     | 0.93%      |
| Xanthogranulomatous cholecystitis | 12      | 02    | 14    | 2.18%      |
| Adenomatous hyperplasia           | 11      | 01    | 12    | 1.8%       |
| Metaplasia                        | 18      | 00    | 18    | 2.8%       |
| Adenomyomatous hyperplasia        | 10      | 0     | 10    | 1.5%       |
| Carcinoma                         | 17      | 02    | 19    | 2.9%       |
| Total                             | 578     | 62    | 640   |            |

All 640 cases underwent histopathological examination. 79.53% cases had chronic inflammation, followed by acute cholecystitis in 8.1%. 2.9% of cases, carcinoma was observed, which was predominantly seen in females.

## DISCUSSION

The incidence of carcinoma Gall Bladder shows widely variable geographic pattern. As compared to western countries incidences of carcinoma Gall Bladder is high in Asia continent with increased incidence in northern India<sup>10</sup> especially in gangetic region of northern India, Pakistani females<sup>11</sup>, and Korean males. Some studies have reported incidence rates ranging from 0.27% to 3.2%.<sup>12</sup> In our study it was 2.9%. One of the study from Eastern India shows incidence rate of 4.29%.<sup>13</sup> Some studies has shown higher incidences up to 6.9% and 7.9%<sup>14</sup> of carcinoma Gall Bladder. Most of the carcinoma of Gall Bladder is diagnosed at late stages due to their vague symptoms. Such patients comes in advanced stages, and shows poor prognosis with a five year survival rate of less than 5%. When detected at early stages, they shows survival rates of 90% to 100%.<sup>15</sup> Many times preoperative diagnosis of carcinoma is not made and are discovered incidentally on cholecystectomy specimen such patients are usually at an early stages and shows best prognosis.<sup>20</sup> The reported incidence of incidental carcinoma varies from 0.35% to 2%.<sup>16</sup>

Cholelithiasis can cause histopathological changes in gall bladder mucosa varying from acute cholecystitis, chronic cholecystitis, xanthogranulomatous cholecystitis, 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.<sup>17</sup> Geography and ethnicity also plays an important role in the prevalence of gall stones.

The incidence of gallstones increases markedly between 41-50 years of age In our study mean age of presentation was 44.16±14.64 years. Our results were in concordance with the results obtained by Khanna et al.,<sup>18</sup> Tyagi et al.,<sup>19</sup> and Singh et al.,<sup>20</sup> who reported the mean age of 42.5, 43.6, and 45.3 years, respectively. 90% of the patients we studied were female. Similar results have been reported in the studies of Mohan et al.,<sup>21</sup> who reported that 86.97% and 86.54% of patients were female, respectively. The age and gender distribution of present as well as previous studies indicate that the incidence of cholelithiasis is higher in adult females. This may be due to decrease in activity of cholesterol reductase and increase in activity of HMG-CoA reductase with age, resulting in increased cholesterol secretion and saturation of bile. The female sex hormones may also expose them to factors that possibly promote the formation of gallstones.<sup>21</sup> We found chronic changes in the form of chronic cholecystitis and chronic cholecystitis with metaplasia being more common histological finding than other changes. Similar findings have been reported in the past who reported preponderance of chronic cholecystitis in gallstone patients in their studies.<sup>21, 19</sup> We observed precancerous lesions (which included both hyperplasia and metaplasia) in 15% of cases. Similar results have been reported in the studies of Stancu et al.<sup>22</sup> and Baig et al.,<sup>23</sup> who have reported the prevalence of hyperplasia in 7.8 and 12.5% of cases, respectively. Mechanical irritation by the calculi could be the possible explanation for these changes as proposed by Elfving et al.<sup>24</sup> Chronic cholecystitis was the most common presentation (79.53%) 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 (56.45%) 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.<sup>25</sup> 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.<sup>26</sup>

Rao et al also reported female Xanthogranulomatous cholecystitis (XGC) is not an uncommon entity and is frequently misdiagnosed as carcinoma of gallbladder. It was detected in 2.10% 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.<sup>27</sup> 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%).<sup>28</sup> 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 2.81% 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.<sup>29</sup> 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.<sup>30</sup> The royal college of pathologists have also recommended routine histopathological analysis of all specimens of gallstones related cholecystectomies.<sup>31</sup>

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.<sup>30</sup> 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.<sup>29</sup> 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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