Is a histopathological examination justified in all cholecystectomy specimens? – A 5 year experience in a tertiary care hospital of Kumaon region in Uttarakhand

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ABSTRACT

Background: Gall bladder specimens are among one of the most common organs received for histopathology examination in any hospital. Gall bladder carcinoma is a malignancy known for being asymptomatic. Our country has experienced a steady increase in the incidence of this malignancy in the recent years. Coexistence of gall stones has lead to the belief that they have a major role to play in the pathogenesis of carcinoma of the gall bladder. Aim: To justify that a histopathological examination should routinely be done for all cholecystectomy specimens. Material and Method: A retroprospective study was done on 1057 gall bladder specimens received over a period of 5 years. Data of the age, sex, clinical findings, provisional diagnosis, and histopathological findings were tabulated into the various histopathological identities. Result: Majority of the histopathological alterations observed in the gall bladder specimens studied including malignancy were not accompanied by gall stones. Conclusion: All cholecystectomy specimens should routinely be sent for histopathological examination irrespective of the presence or the absence of cholelithiasis.

Keywords: Cholecystectomy, cholelithiasis, chronic cholecystitis, females, gall bladder carcinoma.

INTRODUCTION

Gall bladder specimens are one of the most common specimens received for histopathological examination in most hospitals, reason being cholecystectomy is routinely performed by a majority of surgeons for any signs and symptoms indicating gall bladder disease. Women form the bulk of patient population in all gall bladder diseases.

Gall bladder carcinoma was first described by De Stoll in 1777. It is a rare malignancy with marked ethnic, gender, and geographical distribution worldwide. It is a disease known for its rapid evolution and high mortality rate. The only important prognostic factor is the pathological stage of the disease.

Bolivia and Chile have the highest reported incidence rates in the world. The highest mortality rate of both women (16.6/100,000) and men (7.8/100,000) was also observed in Chile. The reports of various Indian registries have revealed a steady increase in the incidence of gall bladder cancer. The incidence rate in India is 2.3 and 1.03 per 100,000 female and male populations, respectively. It is ten times more common in North compared to South India with a particularly high incidence in the Indo Gangetic plain. The high risk regions are a wide band in Northern India encompassing the states of Uttar Pradesh, Bihar, West Bengal, and Assam. The highest ASIR (age standardized incidence rate) of gall bladder cancer for both men (5.3/10,00,000) and women (14.3/10,00,000) have been observed in Kamrup urban

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Gall bladder carcinoma unfortunately is notorious for being asymptomatic in nature and this remains a major hurdle for clinicians and surgeons in the diagnosis and treatment. Incidental gall bladder cancer is discovered in 0.3–2% of all cholecystectomies performed for benign conditions. In Chile, where the mortality for gall bladder cancer is the leading cause of cancer deaths in female population, cholecystectomy is a crucial intervention in lowering gall bladder cancer mortality rates. Chianale and associates and Andia and associates have correlated an increased gall bladder cancer mortality rate with low number of cholecystectomies. In the USA which has moderate incidence rate of gall bladder cancer, Bartlett had observed a lowering of gall bladder cancer mortality rates between 1965 and 1989 which coincides with an increased number of cholecystectomies done during that period.

Chronic cholecystitis is the commonest finding in most specimens and though there have been ample studies done in the past proving its strong association with cholelithiasis, it still dares to present itself even without it (acalculous cholecystitis)

An interesting variety of other mucosal changes are also seen as metaplasias (pyloric type, goblet cell type), dysplasia, hyperplasia, cholesterosis, xanthomatous change, adenomyosis, eosinophilic cholecystitis, follicular cholecystitis, xanthogranulomatous cholecystitis and tubercular cholecystitis.

In comparison to other gastrointestinal malignancies little is known about etiology and pathogenesis of gall bladder cancer. The main difficulty in studying the precursor lesions of this disease is the fact that it’s impossible to perform a follow up because the diagnosis is established after the cholecystectomy. Therefore, the evidence relating these lesions to cancer is invariably determined indirectly. A better understanding of the risk factors for the development of gall bladder cancer and it’s premalignant lesions could help select patients for prophylactic cholecystectomies and hopefully reduce the mortality of this invariably fatal disease.

The observation that the gall bladder presents proper pathological alterations, analysis of histological alterations in cholecystectomy specimens makes an interesting topic of study.

We undertook this study to find out whether it is justified to send all cholecystectomy specimens for histopathological examination or not.

**MATERIAL AND METHODS**

The present work was a retrospective study carried out on 1057 consecutive gall bladders resected during a period of 5 years, from January 2007 to January 2012. Patients who had come to the surgical O.P.D with complaints indicating gall bladder disease and who subsequently underwent cholecystectomy were included in the study. The resected specimens were fixed in 10% Formalin and submitted to the Department of Pathology. Three sections were obtained from the fundus, body, and neck. Additional sections were taken from any abnormal appearing area. Routine tissue processing was done of these sections followed by hematoxylin and eosin staining. Data regarding the age, sex, clinical findings, provisional diagnosis were retrieved from the records. Microscopic findings were noted and all the cases were segregated into different groups on the basis of the following histopathological diagnosis. Two broad categories were made—with or without accompanying gall stones

- Chronic cholecystitis
- Chronic cholecystitis with cholesterosis
- Chronic cholecystitis with metaplasia (which included all varieties)
- Dysplasia
- Xanthogranulomatous cholecystitis
- Eosinophilic cholecystitis
- Follicular cholecystitis
- Carcinoma gall bladder

The following microscopic criteria was used for the diagnosis of the above-mentioned lesions -

**Chronic cholecystitis** – Mucosa shows varying degrees of mononuclear infiltration and fibrosis.

**Cholesterosis** – Aggregates of lipid filled foamy cells present in the tips of villi.

**Metaplasia** – Intestinal metaplasia may show the presence of paneth cells or goblet cells. Pyloric metaplasia is more common and may form microscopic nodules and polyps. The glands resemble gastric pyloric glands and differ from the mucous glands of the gall bladder microscopically and histochemically.
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Dysplasia – Pseudostratification of the epithelium, nuclear crowding, some loss in the architecture, disorganization of the epithelium, nuclear atypia.

Xanthogranulomatous cholecystitis – Clusters of foamy macrophages containing bile and lipid granules as well multinuclear giant cells in dense lymphocytic infiltrates.

Eosinophilic cholecystitis – Massive outpouring of mature eosinophils in the inflammatory infiltrate.

Follicular cholecystitis – Wide spread formation of lymphoid follicles in all layers of the gall bladder.

Carcinoma gall bladder – Malignant glandular structures protruding as a mass into the lumen and/or infiltrating into the wall of the gall bladder (adenocarcinoma), showing varying degrees of differentiation as well as squamous metaplasia (adenosquamous).

Primary papillary hyperplasia – It is defined strictly as a very rare phenomenon in which the gall bladder mucosa is thickened and exhibits villous like folds that are taller than normal and closer together without any distinct nodule formation. The process may be focal, diffuse, or segmental.

Adenomyomatous hyperplasia – It is an exaggerated form of diverticular changes and does not involve epithelial hyperplasia.

Spongiod hyperplasia – It represents a combination of localized hyperplasia with delicate fusion of mucosal projections and tangential sectioning. It’s a common and insignificant phenomenon.

RESULTS

A total of 1057 specimens were studied out of which there were 792 females and 265 males establishing a clear female predominance. Only 470 cases were received with gall stones while the rest were acalculous. Age group ranged from 11 to 90 years with the youngest patient a 13 year male and the oldest was an 88 year old male. Twenty cases of gall bladder cancer were observed [Table 1] with 19 out of them being females, maximum (08) in the age group of 41–50 years. Out of the total malignant case reported majority (nine cases) had no gall stones and six specimens received were already cut open gall bladders without any stones, so it could not be ascertained whether gall stones were present at the time of surgery or not. Therefore, in our study only five cases of gall bladder cancer were observed with gall stones. A large share of the total speci-

| Table 1 Frequency of histopathological alterations studied |
|----------------------------------|----------------|----------------|
| Lesion                           | Number | Percentage |
| Gall bladder carcinoma           | 20    | 1.89%       |
| Chronic cholecystitis            | 733   | 69.3%       |
| Chronic cholecystitis with metaplasia | 137  | 12.96%      |
| Chronic cholecystitis with cholesterol | 64   | 6.05%       |
| Chronic cholecystitis with papillary hyperplasia | 30   | 2.83%       |
| Chronic cholecystitis with spongiod hyperplasia | 20   | 1.89%       |
| Chronic cholecystitis with dysplasia | 12   | 1.13%       |
| Xanthogranulomatous cholecystitis | 11   | 1.04%       |
| Chronic cholecystitis with focal cholestasis with metaplasia | 6   | 0.56%       |
| Follicular cholecystitis         | 5     | 0.47%       |
| Chronic cholecystitis with focal granulomatous change | 5   | 0.47%       |
| Acute cholecystitis              | 5     | 0.47%       |
| Eosinophilic cholecystitis       | 4     | 0.37%       |
| Chronic cholecystitis with focal adenomyomatous change | 3   | 0.28%       |
| Gangrenous cholecystitis         | 1     | 0.09%       |
| Chronic cholecystitis with focal cholestasis with low grade intraepithelial lesion | 1   | 0.09%       |

| Table 2 Distribution of cases of chronic cholecystitis |
|----------------------------------|----------------|----------------|
| Sex                              | Number of cases of chronic cholecystitis with gall stones | Number of cases of chronic cholecystitis without gall stones |
| Male                             | 65              | 97             |
| Female                           | 293             | 278            |

| Table 3 Distribution of chronic cholecystitis with cholesterosis |
|----------------------------------|----------------|----------------|
| Sex                              | Number of cases of chronic cholecystitis with cholesterosis with gall stones | Number of cases of chronic cholecystitis with cholesterosis without gall stones |
| Male                             | 04              | 07             |
| Female                           | 22              | 31             |

| Table 4 Distribution of chronic cholecystitis with metaplasia |
|----------------------------------|----------------|----------------|
| Sex                              | Number of cases of chronic cholecystitis with metaplasia with gall stones | Number of cases of chronic cholecystitis with metaplasia without gall stones |
| Male                             | 10              | 15             |
| Female                           | 54              | 58             |
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**DISCUSSION**

Gall bladder stones have always been held as the culprit for most of the histological alterations including gall bladder cancer. Because there is unfortunately no efficient method to detect gallbladder cancer, a better understanding of the risk factors for gallbladder cancer development and pre-malignant lesions of the gallbladder could help select patients for prophylactic cholecystectomies, and, perhaps, reduce the mortality of this almost invariably fatal disease. There are two important carcinogenesis models known: the adenoma-carcinoma sequence and the metaplasia-dysplasia-carcinoma sequence. The observation that the gallbladder presents proper histological alterations raises the possibility of other carcinogenesis models in the gallbladder.\(^{[10]}\)

Females have always been the target population in most of the gall bladder diseases including cancer of the gall bladder. This has also been observed in our study. Prolonged exposure to female sex hormones (estrogen and progesterone) may be the predisposing factor. Therefore, early menarche, early first pregnancy, multiple pregnancies, and a longer reproductive period are factors that may significantly increase the risk of gall bladder cancer in women.\(^{[14]}\)

Gall bladder cancer has traditionally been associated with gall stones. Although gall stones appear to be the most important risk factor, follow-up studies on asymptomatic gall stone patients for 10–25 years show that less than 1% developed cancer.\(^{[13]}\) In our study we observed that most of our cases which displayed various histological changes

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**Figure 1.** Photomicrograph showing predominantly eosinophilic inflammatory infiltrate in the wall of the gall bladder (H&E, ×100).

**Figure 2.** Photomicrograph showing abundant of foamy macrophages intermingled with lymphocytic infiltrate in the gall bladder wall (H&E, ×100).

**Figure 3.** Photomicrograph showing malignant glandular structures present in gall bladder wall along with dense inflammatory infiltrate (H&E, ×100).
as well as cases of cancer were not accompanied by gall stones which is contrary to the study done by Khanna et al\textsuperscript{[1]}. Also, if we were to assume that stones on chronic inflammation were responsible for the development of cancer, then one would expect squamous cell carcinoma to be the morphological type of carcinoma developing not adenocarcinoma which is frequently seen in these cases. So, though the association of gall stones with carcinoma is frequently observed we could assume that they have a facilitative role to play but they definitely are not solely responsible for the malignant transformation in the gall bladder epithelium. In our study, the incidence of carcinoma is only 1.89\% which is definitely low considering the fact that we come in the high incidence region of the country. The low incidences of all studied histological alterations including gall bladder cancer could be explained by the fact that all the gall bladders were submitted to a routine histopathological examination with only three histological segments (the fundus, body, neck) and any observed macroscopic alterations. According to Albores-Saavedra and Henson (1986), the incidence of histological alterations in chronic cholecystitis is generally a reflection of the number of histological segments analyzed and the technique used. They report that when multiple sections of the gallbladder are examined, dysplasia and carcinoma \textit{in situ} are observed in 13.5\% and 3.5\% of patients, respectively.\textsuperscript{[2]} Additionally, a larger population sample would probably also affect the results of this study. Flum and associates, who used 1500,000 patients who underwent laparoscopic cholecystectomy to study the effect of intraoperative cholangiography \textit{per se} in preventing common bile duct injury during cholecystectomy, argue that infrequent events can only be detected in large samples of population.\textsuperscript{[3]}

In our study, metaplasia was seen predominantly in women which is also reported by Duarte and associates.\textsuperscript{[4]} Adenomyomatosis, a non-inflammatory gall-bladder alteration, occurs in middle age patients, and the incidence increases with age. Originally depicted as a benign finding, it is currently identified as a premalignant lesion, and cancer cases associated with areas of adenomyomatosis have been reported.\textsuperscript{[5,6]} In this study, a higher incidence of adenomyomatosis within elderly patients and women has been observed, similar to other studies. Xanthogranulomatous cholecystitis is an uncommon inflammatory and destructive gall bladder process that can spread to adjacent structures and be confused with cancer.\textsuperscript{[7]} Similar to adenomyomatosis, xanthogranulomatous cholecystitis presented a higher incidence within elderly individuals in this study and again occurred more often among women. Interestingly in our study, adenomyomatosis, pyloric metaplasia, intestinal metaplasia, and dysplasia were observed in acalculous patients, which goes on to prove that potentially serious lesions could be present in patients with few or no symptoms.

CONCLUSION

In our study we found that majority of histological alterations of the gall bladder including carcinoma were seen more frequently without gall stones.

This brings us to the crucial question that should all cholecystectomies performed for patients with gall bladder disease be sent for histopathological examination especially in a country like ours which has limited resources? The data presented in this study clearly reflects that gall stones should not be the sole criterion for sending for a histopathological examination as even without cholelithiasis the gall bladder can host a variety of histological changes including carcinoma. Therefore, it is recommended that all cholecystectomy specimens should be routinely sent for histopathological examination. The belief that gall stones are a predisposing factor for gall bladder cancer still remains in doubt. Nonetheless, further studies are required to understand gall bladder carcinogenesis which is crucial for establishing surgical treatment for not only gall bladder cancer but also for all pathological conditions of the gall bladder both with and without gall stones.

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