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Original Article

Incidental Finding of Gall Bladder Carcinoma in Post-Menopausal Females in Cholecystectomy Specimen

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ABSTRACT

Objective: To highlight the significance of histopathological examination of gallbladder and to evaluate incidental gallbladder cancer in post-menopausal females.

Study Design: Cross-sectional Study.

Place and Duration of Study: Department of Pathology, Diagnostic and Research Laboratory, Liaquat University of Medical and Health Sciences, Hyderabad Pakistan, from Jan 2020 to Dec 2021.

Methodology: Two thousand nine hundred fifty-nine (n=2959) gallbladder specimens with a clinical diagnosis of cholelithiasis and cholecystitis were analyzed. The clinical history of patients was taken from computer storage data.

Results: Out of the total 2959 cases, on histopathological examination, chronic cholecystitis was the commonest finding (1990, 67.25%), followed by acute cholecystitis 410(13.85%) cholesterolosis (396,13.38%) and gallbladder carcinoma 42(1.42%). Out of 42 cases of gallbladder carcinoma, 34(80.95%) were female and 8(19%) were male. Most cases were post-menopausal age group 21(61.76%) compared to premenopausal 13(38.23%).

Conclusion: In our study, Incidental gallbladder carcinoma in post-menopausal women was higher than expected.

Keywords: Cholecystectomy, Cholelithiasis, Gall bladder carcinoma, Post-menopausal females.

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INTRODUCTION

Cholecystectomy is one of the most commonly performed surgical procedures today due to the high incidence of gallstones in the population. In certain cases, cholecystectomy specimens uncover such incidental findings, which, if overlooked, can prove catastrophic.[1] Gallbladder carcinoma is a well-known gastrointestinal cancer yet remains a diagnostic challenge for clinicians as its presentation can be nonspecific and is typically asymptomatic in the initial course of the disease. It is frequently seen as an incidental finding in histopathologic examination of cholecystectomy specimens. The histopathologic examination of the gallbladder is mandatory to stage the disease and initiation of treatment accordingly.[2,3]

Pathologic examination of all cholecystectomy specimens is a long-established procedure.[4] Few recent studies have invalidated this practice, considering selective histopathologic examination a practicable and safe approach. Pathologic examination of an otherwise normal gallbladder is often neglected and considered unnecessary as it is assumed to be unremarkable. Gallbladder cancer is often an incidental finding in cholecystectomy specimens, and its misdiagnosis can be detrimental.[5,6] Gallbladder cancer carries a dreadful prognosis with frequent progression from metaplasia to dysplasia and carcinoma in situ to invasive carcinoma. 5-year survival statistics of Gallbladder cancer indicate a mean survival rate of only six months.[7] Early diagnostic strategies aid in improving outcomes and, consequently, improve survival rates in patients.

The mean age at menopause in Pakistan is 47 years.[8] The incidence of gallbladder cancer is more common in the female population due to its association with female hormones.[9] Women are at two to six times more risk of developing gallbladder cancer than males. The female hormone estrogen level correlates with an increased incidence of gallstones as it causes the saturation of cholesterol in bile and is hence believed to be the main offending agent in gallbladder cancer in females.[10]

This study was designed to highlight incidental findings of gallbladder carcinoma in patients with no prior suspicion of malignancy and to elaborate on the significance of histopathologic examination in cholecystectomy specimens.

METHODOLOGY

The cross-sectional study was carried out at the Department of Pathology, Liaquat University of Medical and Health Sciences Jamshoro Sindh Pakistan, for two years from January 2020 to December 2021.

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This study was approved by the Institutional Review Board (LUMHS/DEAN/BMS/-18). The sample size was calculated by Open Epi software taking prevalence of gallbladder cancer in Pakistan as 1.8%.[10]

Inclusion Criteria: All cholecystectomy specimens with a clinical diagnosis of cholelithiasis and cholecystitis received at the department of pathology were included.

Exclusion Criteria: Cholecystectomy Specimen with autolytic changes and metastatic carcinoma were excluded.

The female population was divided into two groups: pre and post-menopausal. Women aged 47 years and above were included in the post-menopausal group. The patient's clinical history was taken, and histopathological reports were recovered from computer data storage. Microscopic slides were taken from the Department of Pathology. Two histopathologists examined the slides to confirm the diagnosis.

All the statistical analysis was carried out at the Statistical Package for the Social (SPSS) version 22. Mean and standard deviation were calculated for quantitative variables like age and number of diagnoses. Frequency and percentage were calculated for qualitative variables such as histopathological findings. The chi-square statistic was used for inferential statistics. The *p*-value of ≤0.05 was considered significant.

RESULTS

Of the 2959 patients, 587(19.83%) were male and 2372(80.16%) were females. Chronic cholecystitis was the most common finding in the histopathological examination, with 1990(67.25%) cases. Gallbladder carcinoma was found in 42 cases (1.4%), with a higher occurrence in females 34(80.95%) as compared to males 8(19.04%). The gender-wise distribution of histopathological findings is shown in Table-I.

Table-I Distribution of Histopathological Findings with respect to Gender (n=2959)

Histopathological Findings	Female	Male
Chronic Cholecystitis	1631(81.95%)	359(18.04%)
Acute Cholecystitis	276(67.3%)	134(32.68%)
Cholesterolosis	342(86.4%)	54(13.6%)
Carcinoma	34(81.0%)	8(19.0%)
Empyema	26(70.3%)	11(29.7%)
Intestinal Metaplasia	27(84.4%)	5(15.6%)
Adenomyomatous Hyperplasia	17(68.0%)	8(32.0%)
Xanthogranulomatous Cholecystitis	16(66.7%)	8(33.3%)
Biliary Intraepithelial Neoplasia	3(100.0%)	0(0.0%)

Gallbladder carcinoma, and biliary intraepithelial neoplasia was more frequent in older ages, as most cases were found in the sixth decade, as shown in Table-II. Adenocar-cinoma was the most common finding among all cases of carcinoma, predominantly in post-menopausal females 21(61.76%). Moreover, it was significant (*p*-value<0.05) in post-menopausal women than in premenopausal women, as shown in Table-III.

Table-II: Distribution of Histopathological Findings with respect to Mean Age in Females (n=34)

Histopathological Findings	Mean±SD
Adenomyomatous Hyperplasia	35.58±11.63 years
Cholesterolosis	38.40±10.91 years
Chronic Cholecystitis	40.45±12.75 years
Acute Cholecystitis.	43.43±12.92 years
Empyema	43.61±9.97 years
Intestinal Metaplasia	44.22±11.22 years
Xanthogranulomatous Cholecystitis	42.81±9.98 years
Gall Bladder Carcinoma	51.05±13.03 years
Biliary Intraepithelial Neoplasia	60.00±5.00 years

Table-III: Distribution of Gallbladder Carcinoma with respect to Menopausal Status (n=2372)

Menopausal status	Gallbladder Carcinoma		*p*-value
	Carcinoma	Non-carcinoma	
Premenopausal	13(0.78%)	1645(99.21%)	1.000
Postmenopausal	21(2.89%)	705(97.10%)	<0.001

DISCUSSION

This study has analyzed the incidental finding of gallbladder carcinoma and its association with gender and age groups and compared our findings with other studies conducted worldwide. Routine histopathological examination for all specimens is still a topic under debate. Symptomatic cholelithiasis is the most common reason for cholecystectomy all around. However, histopathological examination of all gallbladder specimens is advised as it may uncover multiple findings such as cholecystitis, cholesterolosis, adenomyomatous hyperplasia, intestinal metaplasia and invasive carcinomas.[11]

Gallbladder cancer is a lethal gastrointestinal tract malignancy and has poor survival.[12] Agarwal *et al*.[13] reported that GBC patients whose cholecystectomy specimens were sent for histopathological analysis had better overall survival than those whose specimens were neglected and presented late, with poor resectability rate and worse outcomes.

Few studies consider selective histopathological examination a reasonable strategy if the surgeon carefully examines the specimen before sending it for

histopathology. As cholecystectomy is a routinely performed surgical operation, it will be a cost-effective approach in economically underdeveloped countries and countries with low incidence rates of gallbladder carcinoma. However, it cannot be adopted as a preferred approach universally.[14–16]

According to our study, incidental gallbladder carcinoma was higher in females in the late 4th and fifth decade of life than in males. This gender bias in our data warrants a comprehensive analysis of the role of female hormones in the pathogenesis of gallbladder carcinoma. Young age at menarche, adolescent pregnancy, multiparity and late menopause conclusively prolongs estrogen level in females and is identified as the main culprit in gallbladder carcinoma in females.[17] Recalde *et al*. reported a positive association of obesity with an increased risk of gallbladder cancer.[18] Lundgren *et al*. reported that a high proportion of incidental gallbladder cancer was found in specimens submitted without any selective approach. Most of the cases were of old-age females.[19]

Our study found 60 (2.02%) cases of premalignant lesions such as intestinal metaplasia, adenomyomatous hyperplasia, and biliary intraepithelial neoplasia. Additionally, we analyzed GBC in various age groups, and a higher rate of GBC was found in post-menopausal females as compared to premenopausal. Dubey *et al*.[20] Dutta *et al*.[21] and Alkhayyat *et al*.[22] also reported the same in their studies.

Therefore, a careful inspection of gallbladder specimens and a proper clinical history of patients must be taken to diagnose gallbladder carcinoma in females. As gallbladder carcinoma is a very aggressive disease, the overall survival of patients can be improved with early detection of the tumour. We can conclude that all gallbladder specimens of old-age women, particularly post-menopausal, must be sent for a histopathological examination so that any worse outcome can be avoided in future.

CONCLUSION

We have found that a careful and detailed histopathological examination should be adopted for gallbladder specimens, as the consequences of missing incidental gallbladder cancer can be immense. A high proportion of gallbladder cancer in post-menopausal females warrants a comprehensive analysis of cholecystectomy specimens. In order to improve the long-term outcome and severity of the disease, removal of gall bladder should not be delayed in post-menopausal women on provisional clinical diagnosis of cholecystitis, and the specimen must be sent for histopathological examination for final diagnosis as they are at six times more risk of developing carcinoma.

Conflict of Interest: None.

Author's Contribution

Following authors have made substantial contributions to the manuscript as under:

PK: & MRK: Data acquisition, data analysis, critical review, approval of the final version to be published.

MA: & RAM: Study design, drafting the manuscript, data interpretation, critical review, approval of the final version to be published.

ZA: & IDU: Concept, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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