Original Article

UNEXPECTED GALL BLADDER CARCINOMA – A SURPRISING HISTOPATHOLOGICAL DIAGNOSIS

Sahar Iqbal[1], Fariha Sahrish[1], Samra Sameen[2], Firdous Iqbal[1], Sarosh Aitzaz[3], Sara Masood Cheema[1]

[1]Azra Naheed Medical College, Lahore Pakistan
[2]Services Hospital, Lahore Pakistan
[3]Abbottabad International Medical College, Abbottabad Pakistan

ABSTRACT

Objective: To determine the frequency of gall bladder carcinoma incidentally diagnosed in patients undergoing routine laparoscopic cholecystectomy.

Material and Methods: Histopathology section of Pathology Department, Azra Naheed Medical College Raiwind Road, Lahore from January 2018 to July 2021. A total of 214 simple or laparoscopic cholecystectomy specimens were included. Detailed gross & microscopic examination was done. All diagnoses including benign histopathological findings and incidental gall bladder carcinoma were analyzed. The important findings like resection margin involvement, maximum wall thickness of gallbladder, type of adenocarcinoma and TNM staging were noted.

Results: Out of 214 simple or laparoscopic cholecystectomy specimens, there were three (1.4%) cases of incidental gallbladder carcinoma exclusively found in females. Mean age recorded was 45.7 years. Maximum thickness of gall bladder wall was 4.7 cm and maximum stage was pT2.

Conclusion: According to our study there were three cases of incidental gallbladder carcinomas out of 214 cholecystectomy specimens. Considering this, histopathological study of gall bladder is essential not to miss any carcinoma, keeping in view the grim prognosis.

Key Words: Gall bladder, Incidental carcinoma, Cholecystectomy, Cholelithiasis.

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INTRODUCTION

Gall bladder carcinoma (GBC) is an infrequent Gastrointestinal (GI) neoplasm with rapidly progressive clinical course and fatal outcome despite diligent treatment. It is the 5th most common malignancy of the GIT and in the biliary tract it is the most frequent malignant neoplasm. GBC is more commonly seen in females as compared to males [1]. GBC is highly prevalent among the age group of 50 to 70 years.[2] Due to the vague clinical presentations the neoplasm is diagnosed at an advanced stage which results in a survival rate of less than 5% hence causing grim prognosis [2]. Majority of the malignant cases (85%) are linked with Cholelithiasis. However, no definite pathogenetic relationship can be proven except that porcelain gall bladder is a precursor lesion to malignancy [3].

Preoperatively only 30% GBC are suspected whereas almost 70% are incidentally diagnosed either during intraoperatively or during routine histopathological examination (HPE) [2]. Globally, the recommended gold standard management of gall bladder disease is laparoscopic cholecystectomy (LC) owing to proficient results in post-operative patient care [4]. GBC is infrequent in LC specimens received for benign gall bladder diseases [4]. Regardless of all modern radiological modalities, early-stage tumors are difficult to diagnose because of indeterminate presenting complaints and nonspecific clinical findings [4,5]. Incidental gall bladder carcinoma (IGBC) refers to GBC not suspected clinically, or during cholecystectomy procedure and accidently found on routine HPE for the first time [5]. Clinical outcomes of IGBC are one step ahead of GBC which carries dismal prognosis. In comparison to poor prognosis of already diagnosed gall bladder carcinoma, outcomes of IGBC are quite satisfactory [5] The reason being the detection of IGBC at early stage & simple cholecystectomy is usually considered sufficient depending upon tumor stage [4].

Incidence of IGBC is reported between 0.2-2.8% and varies in different geographic regions of the world [2]. It is recommended to submit all routine cholecystectomy specimens for HPE so that any occult pathologies are not overlooked [6]. Studies conducted by Royal College of Pathologists have shown that all cholecystectomy specimens should be

Correspondence: Dr. Sahar Iqbal, Assistant Professor, Department of Histopathology, Azra Naheed Medical College Lahore Pakistan

Email: **sahar_moeed@hotmail.com**

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submitted for histopathological evaluation as many significant pathologies including malignancy can present with nonalarming clinico- radiological findings [4,6,7]. However, with the ever-increasing workload in histopathology departments and associated expenses the need for HPE of routine cholecystectomy specimens is often being challenged [8].

The rationale for conducting this study is that the diagnosis of incidental gall bladder carcinoma can be easily missed in those patients whose gall bladder specimens are not sent for histopathological examination. Furthermore, it will emphasize how a vigilant gross examination of cholecystectomy specimens are essential to pick any suspicious areas like abnormal wall thickening or nodularity.

Keeping in view the background literature, we are reporting our experience of GBC diagnosed incidentally on HPE of routine cholecystectomy specimens performed for cholelithiasis or cholecystitis received at our histopathology department.

Inclusion criteria: Patients of all ages, both genders, patients with simple open & laproscopic cholecystectomy specimen as well as previously incised & fragmented specimens were included.

Exclusion criteria: Radical cholecystectomy with liver resection and lymphadenectomy specimen, cholecystectomies done for metastatic disease, autolyzed specimens and blocks received for review were excluded.

MATERIAL AND METHODS

This was a retrospective cross-sectional study approved by ethical review board vide letter # IRB/ANMC/2021/0003 conducted at histopathology department of Azra Naheed Medical College Raiwind Road Lahore between January 2018 to July 2021. Total of 214 specimens were estimated by 95% confidence interval and 35+/- standard deviation calculated by sample size calculator $n = 1.96^2@^2/E^2$. Detailed history and basic lab investigations were obtained from the patient files. Specimens were received fixed in 10% neutral buffered formalin. Comprehensive gross examination was carried out for any abnormal wall thickening or growth. In cases of suspected carcinomas, specimens were meticulously sectioned as per protocol of American College of Pathologist. Cystic duct resection margin and liver parenchymal resection margin were inked and evaluated for tumor involvement. After sectioning resection margins, extensive sampling of grossly thickened areas was done to determine type and pTNM staging of carcinoma.

Tissue sections were processed in the automatic tissue processor with overnight dehydration by ethyl alcohol, cleared by xylene, impregnated with paraffin wax, followed by paraffin blocks preparation and H&E-stained slides were prepared.

Statistical analysis was done on Statistical Packages of Social Sciences (SPSS) version 23. Qualitative variables like age, gender, histopathological diagnosis, wall thickness, tumor subtypes and staging were summarized as frequencies and percentages. No statistical association was determined between any variables.

RESULTS

A total of 214 cholecystectomy specimens were received from Jan 2018 to July 2021 with a male to female ratio of 1:4 comprising 43 (20.1%) males & 171 (79.9%) females as shown in Table-I. The age range was 16 years to 81 years and mean age was 45.7 years. Out of 214 cholecystectomies, 211 cases were non-neoplastic lesions. Histopathological diagnostic breakup with gender distribution is summarized in Table I. There were 3 (1.4%) cases of incidental gall bladder carcinoma diagnosed during routine histopathological examination (Table-II).

Chronic cholecystitis with cholelithiasis comprised the main bulk of benign gall bladder pathological diagnosis (n=130,60.5%) predominantly seen in females (n=105,61.4%) as shown in Table I. p value calculated by Chi square test is 0.846 and 0.947 (<0.05) showed no statistical association of gall bladder diseases with gender and age group. Majority cases (n=135, 63.0 %) showed wall thickness of more than 3 mm. Few cases showed wall thickness of more than 10 mm (n=11,5.2%), including cases of malignancy.

Three cases of gall bladder adenocarcinoma (n=3, 1.4%) were diagnosed incidentally. All cases were females and diagnosed in the 5th to 7th decade of life. Preoperative diagnosis of these patients was chronic Cholecystitis with cholelithiasis. Detailed clinico-histopathological description of IGBC is summarized in Table-II and shown in Figure-I and Figure-II.

No case of dysplasia in adjacent mucosa and Intracholecystic papillary neoplasm was noted histologically in our study.

Table-I: Gender specified histopathological diagnosis breakup of cholecystectomy specimens.

Histological Diagnosis	n (%)	Male (%)	Female (%)
Chronic Cholecystitis with Cholelithiasis	130 (60.5)	25(5)	105(61.4)
Chronic Cholecystitis	44(20.5)	11(25.5)	33(19.2)
Acute on Chronic Cholecystitis with Cholelithiasis	18(8.4)	3(6.9)	15(8.77)
Chronic Cholecystitis with Cholelithiasis and cholesterolosis	9(4.2)	2(4.65)	7(4.09)
Xanthogranulomatous Cholecystitis	5(2.3)	2(4.65)	3(1.7)
Incidental Malignancy	**3(1.4)**	**0(0)**	**3(1.7)**
Follicular Cholecystitis with Cholelithiasis	2(0.9)	0(0)	2(1.1)
Empyema Gall Bladder	2(0.9)	0(0)	2(1.1)
Adenomyomatous Hyperplasia associated with Chronic Cholecystitis with Cholelithiasis	1(0.5)	0(0)	1(0.5)
Total	**214 (100%)**	**43 (20.09%)**	**171 (79.9%)**

Table-II: Clinicopathological features and pathological staging of Incidental gall bladder carcinoma

Sr #	Age	Gender	Imaging finding	Surgery	Macroscopic appearance	Tumor Type	TNM stage
1	55	female	Thickened wall	Laparoscopic cholecystectomy	Diffuse wall thickening 3.8cm	Moderately differentiated adenocarcinoma	pT2a
2	70	female	Thickened wall	Laparoscopic cholecystectomy	4.7 cm papillary fronds	Moderately differentiated adenocarcinoma	pT1b
3	56	female	Normal	Laparoscopic cholecystectomy	1.5 cm, Wall thickening	Moderately differentiated adenocarcinoma	pT2a

Table-III: List of some national and international studies sowing frequency of incidental gall bladder carcinoma

Studies	Duration	Place of study	Sample size	Mean age	M:F	Frequency of IGBC (%)
National studies						
Iqbal *et al* - current study	2018-2021	Lahore	214	45.7	1:4	1.4
Tanveer SM *et al*[11]	2009-2015	Rawalpindi	10549	52.48	1:2.3	1.55
Manzoor A *et al*[12]	2012-2014	Islamabad	940	68.5	1:1	0.21
Khan *et al*[13]	2008-2010	Rawalpindi	500	45	0:1	0.20
Siddiqui *et al*[16]	2010-2012	Hyderabad	220	32.3	1	2.8
Qazi *et al*[25]	2009-2011	Kohat	200	52.57	1:7	4.0
Shah *et al*[9]	2008-2011	Peshawar	260	55.25	1:10	4.23
International studies						
Yi *et al*[27]	2013-2006	China	14073	58	1:3.75	0.18
Kalita *et al*[28]	2012-2009	India	4115	54	0.87:1	0.44
Jetley *et al*[29]	2012-2007	India	622	53	0:6	0.96
Ghnnam *et al*[30]	2012-2007	Egypt	1892	73.6	2:8	0.5

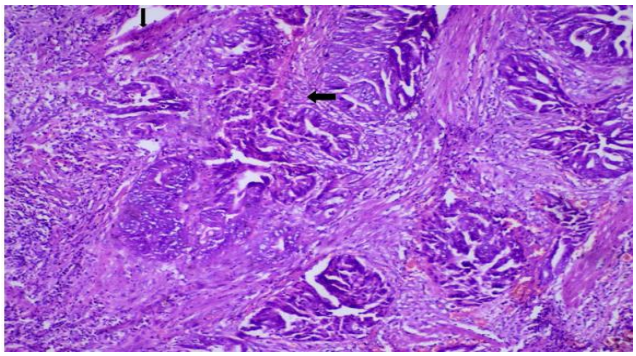

Figure-I: Photomicrograph shows neoplastic cells arranged in nests and tubules present in gall bladder wall, Moderately Differentiated Adenocarcinoma, pT2 (arrows) X 20.

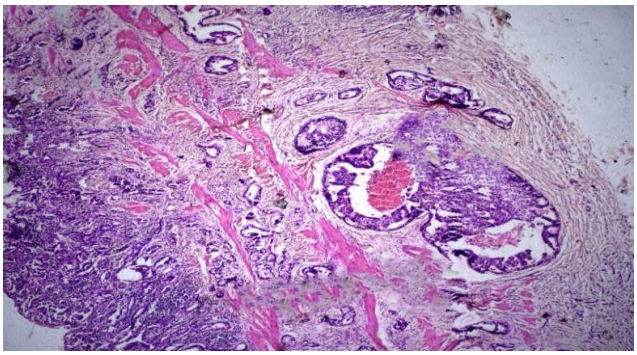

Figure-II: Photomicrograph shows neoplastic cells invading gall bladder wall, moderately differentiated adenocarcinoma, pT2 (arrows) X 20.

DISCUSSION

Gall bladder malignancy is relatively an uncommon clinical finding. Clinical presentations are quite overlapping with benign gall bladder pathologies, hence the reason for late diagnosis. Consequently, the prognosis of GBC becomes worse. More often diagnosis remains unrevealed even after detailed investigations including radiological studies. This is not an uncommon scenario where GBC is diagnosed incidentally intraoperatively or during histopathological diagnosis of routine LC specimens [1-8].

The mean age reported in our study was 45.7 years, comparable to other studies reported by local author Khalid *et al* [17] and Digvijay *et a* [14]. A local author Abbasi showed slightly higher mean age of 47.7 years [20]. Turkish author Murat *et al* showed mean age 60.85 years [2] and in an Islamabad based study Manzoor *et al* and Tanveer *et al* reported mean age 68.5 and 59.23 years respectively, higher than our study [11,12].

In our study all three patients with incidental diagnosis of malignancy were females similar to the study done by Turkish author Murat *et al* [2], Pitt *et al* [9] & local study by Abbasi *et al* [20]. Other studies also showed clear female preponderance including 1:3 reported by Devnand *et al* [18], 1:7 in a national study reported by Faisal *et al* [16]. Interestingly Manzoor *et al* showed equal male to female ratio 1:1 [12].

Literature search showed vide variations in national and international studies in the incidence of IGBC as shown in Table-III. Our study showed the frequency of incidental gall bladder carcinoma is 1.4%, another local study by Tanveer *et al*. reported incidence of IGBC (1.5%), which is very close to our study [11].

However, some local authors reported much lower incidence such as 0.20% by Manzoor *et al* [12] and 0.21% by Khan *et al* [13]. Neighboring country India reported similar lower observations such as 1.14 % by Vikash *et al* [15], 0.3 % by Weinstein [21], 0.6% by Tantia *et al* [22] & Digvijay *et al* [14] and, 0.8 % by Solaini L *et al* [10], 0.96 % by Sujata *et al* [4]. A study conducted at Agha Khan Hospital Karachi by Samad *et al* showed 1.15% [19]. A Turkish author Kanlioz *et al* observed low incidence of IGBC 0.14% [2]. Other international authors reported much lower incidence as shown in Table-III.

Whereas some studies showed higher incidence of IGBC, Rommohan *et al* 53.2% [26] Siddiqui *et al* showed 2.8% [16], Khalid *et al* reported 6.1% [17], 5.21 % by Siyal *et al* [23] 6.9% by Nawaz *et al* [24] and Qazi *et al* 4% [25] in their studies. The time span in which these studies were conducted was more than our study time period.

In our study majority of cases showed moderately differentiated adenocarcinoma subtype comparable to local and international authors Tanveer al [11], Siddiqui *et al* [16] and Vikash *et al* [15]. In contrast Shrestha *et al* [10] and Manzoor *et al* [12] showed poorly differentiated carcinoma. Wheareas Khan *et al* showed one case of carcinoma in situ only [13].

In the current study majority tumors were stage pT2 comparable to Vikash *et al* [15]. Wheareas in contrast Tanveer *et al* [11], Manzoor *et al* [12] reported majority pT3 tumors. Khan *et al* [13] reported Tis and Siddiqui *et al* [16] reported predominantly pT1b tumors.

CONCLUSION

Despite latest advances in technology, the clinico-radiological findings at an early stage are quite deceptive and clinically carcinoma can be easily missed. So histopathological analysis of all gall bladder specimens is highly essential. A comprehensive clinical history, strong radiological correlation with detailed histopathological evaluation is the mainstay of early diagnosis and good prognosis.

AUTHOR CONTRIBUTION

Sahar Iqbal: Conception and design study
Fariha Sahrish: Literature search and data collection
Samra Sameen: Data analysis
Firdous Iqbal: Data interpretation
Sarosh Aitzaz: Manuscript drafting
Sara Masood Cheema: Revision of intellectual content

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