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Original Article

Carcinoma Involving Gall Bladder: A Four Year Study in a Tertiary Care Hospital in Kashmir Valley

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Abstract

Background: Carcinoma of gall bladder clinically mimics benign gall bladder diseases and often escapes detection until advanced stage. Careful attention to any evidence of wall thickening, thorough sampling and close examination of any deeply situated glandular structures are critical.

Aims: To study the clinicopathological pattern of gall bladder malignancies.

Materials And Methods: This was a 4 year retrospective study and carried in Department of Pathology, Government Medical College, Srinagar, Kashmir, between January 2015 and December 2018. Our study included 57 cases of gall bladder malignancies including incidental detected cases.

Results: During this four year study, a total of 57 patients were studied. Male to female ratio of 0.78:1 was seen. The age of the patients ranged from 27-85 years and peak age incidence was seen in sixth decade of life. The most common presenting symptoms were pain abdomen followed by anorexia and dyspepsia. Grossly evident tumor was seen on initial pathologic examination in 49 cases (85%) while 8 cases grossly presented no visible tumor (i.e. incidental gall bladder carcinomas having only mild wall thickening undetected by imaging).The most common tumor sites were in the body and the fundus of gallbladder. The most common histologic type was adenocarcinoma NOS in 47 cases followed by papillary adenocarcinoma in 2 cases, mucinous adenocarcinoma in 2 cases, primary squamous cell carcinoma in 3 cases, and a single case each of neuroendocrine tumor and adenosquamous carcinoma. Immunohistochemistry was done, wherever needed, for confirmation.

Conclusion: GBC is not an uncommon clinical entity in Kashmir valley, unlike western countries. In spite of the advanced imaging techniques, early gall bladder carcinoma is not efficiently detected. Therefore, every gallbladder should be subjected to routine histopathological examination because with identification of an early gallbladder carcinoma a curative resection may be possible and these patients have a good long term survival.

Key words: Gall bladder, Carcinoma, Cholelithiasis, Polyp, Bile reflux

INTRODUCTION

Gallbladder cancer (GBC) is a rare malignant neoplasm.[1] It is, however, the most common malignancy of the biliary tract and sixth in overall gastrointestinal cancer incidence.[1,2] Gallbladder carcinoma is 2–6 times more common in women than men. Incidence increases with age and >75% of patients with this malignancy are older than 65 years.[3] Since early symptoms are vague and anatomically the gallbladder lacks a serosa to limit cancer spread, the diagnosis of GBC frequently occurs at an advanced stage, typically with an abysmal prognosis. Its 5-year survival rate is <5% for more advanced stages. The overall mean survival rate for patients with GBC is 6 months.[4] According to literature, 30% of cases are not confirmed before surgery. Other cases are detected incidentally by histopathology. Clinical trials and meta-analyses show that incidental GBC occurs in 0.19%–2.8% of patients after cholecystectomy.[5] Predisposing conditions for GBC include chronic gallstones, chronic infections leading to cholangitis (e.g., *Salmonella enteric* typhi and *Helicobacter pylori* seen mainly in India and Bangladesh), porcelain gallbladder, Mirizzi's syndrome, bile

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reflux, and gallbladder polyps.[6] Cholelithiasis is found in approximately 85% of people with GBC. The association between cholelithiasis and GBC ranges from 2.3 to 34.4 in case–control studies[7] The present study was conducted to study the clinicopathological pattern of gallbladder malignancies.

MATERIALS AND METHODS

Table 1: Year-wise distribution of patients (*n*=57)

Year	GBC cases
2015	11
2016	10
2017	23
2018	13
Total	57

GBC: Gallbladder cancer

Table 2: Distribution of age of patients (*n*=57)

Age	*n* (%)	Male	Female
10–20	-	-	-
21–30	1 (1.75)	-	1
31–40	3 (5.26)	-	3
41–50	8 (14)	5	3
51–60	17 (29.8)	8	9
61–70	21 (36.8)	6	15
71–80	6 (10.5)	5	1
81–90	1 (1.75)	1	-
Total	57	25	32

Table 3: Gross morphology in 57 resected specimens

Site	Number (%)
GB mass lesion	
Body	18 (31.5)
Fundus	14 (24.5)
Infundibulum/neck	7 (12.2)
Whole GB	4 (7.01)
GB wall thickening only	14 (24.5)
Total	57

Table 4: Histopathological findings in 57 resected surgical specimens

Histopathological variants	Number (%)
Adenocarcinoma not otherwise specified	48 (84.2)
Moderately differentiated	29 (61.7)
Well differentiated	15 (31.9)
Poorly differentiated	4 (8.5)
Mucinous adenocarcinoma	2 (3.5)
Papillary adenocarcinoma	2 (3.5)
Squamous cell carcinoma	3 (5.2)
Adenosquamous carcinoma	1 (1.7)
Neuroendocrine tumor	1 (1.7)
Total	57 (100)

The present hospital-based study was done retrospectively within a period of 4 years (January 2015–*December* 2018) in the Department of Pathology Government Medical College, Srinagar, Kashmir. All the patients diagnosed with primary carcinoma of gallbladder including incidentally diagnosed gallbladder carcinomas were included in our study. The total number of cases was 57. Paraffin-embedded Hematoxylin and Eosin stained tissue sections were analyzed by a group of histopathologists to reach a morphological diagnosis. Immunohistochemical analyses were performed, wherever required, on the paraffin-embedded tissue sections using a panel of monoclonal antibodies.

RESULTS

During this 4-year study, a total of 57 patients were studied [Table 1]. Males contributed 25 cases (43.8%) and females 32 cases (56.14%), with a male to female ratio of 0.78:1 [Table 2]. The age of the patients ranged from 27 to 85 years. The peak age of presentation was the sixth decade of life [Table 1]. The presenting symptoms were abdominal pain, anorexia, dyspepsia, weight loss, jaundice, nausea, vomiting, malaise, and pruritis. Imaging (ultrasound [USG]/computed tomography [CT]/magnetic resonance imaging) was done in all the patients who mostly revealed a polypoidal mass projecting into the lumen of the gallbladder with the absence of acoustic shadowing or an asymmetric thickening of the gallbladder wall. However, incidental gallbladder carcinomas constituted 8 cases (14.02%) which were not detected on imaging. Gallstones were present in 50 cases (87.7%). The diagnostic accuracy of USG is over 80% in detecting carcinoma gallbladder.[8] Laboratory investigations revealed anemia (Hb <12 g/dl) in most of the patients and leucocytosis (TLC >10,000/mm^3). Grossly evident tumor was seen on initial pathologic examination in 49 cases (85%) while 8 cases grossly presented no visible tumor (i.e., incidental gallbladder carcinomas having only mild wall thickening undetected by imaging). The most common tumor sites were in the body and the fundus of the gall bladder [Table 3]. Surgical specimens from the 57 patients showed adenocarcinoma NOS in 47 cases, papillary adenocarcinoma in 2 cases, mucinous adenocarcinoma in 2 cases, primary squamous cell carcinoma in 3 cases, and a single case each of neuroendocrine tumor and adenosquamous carcinoma [Table 4]. Immunohistochemistry was done, wherever needed, for confirmation. Staging of the patients was done according to AJCC TNM 7th edition: Stage I in 20 patients (%), Stage II in 30 patients (%), and Stage III in 7 patients (%). In addition, xanthogranulomatous cholecystitis was found in 3 cases.

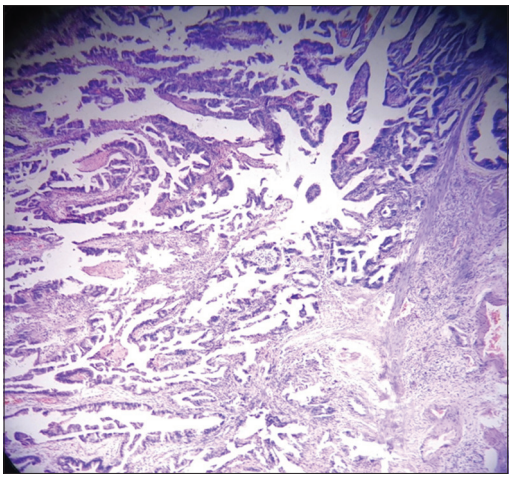

Figure 1: Photomicrograph of adenocarcinoma gallbladder (low power view)

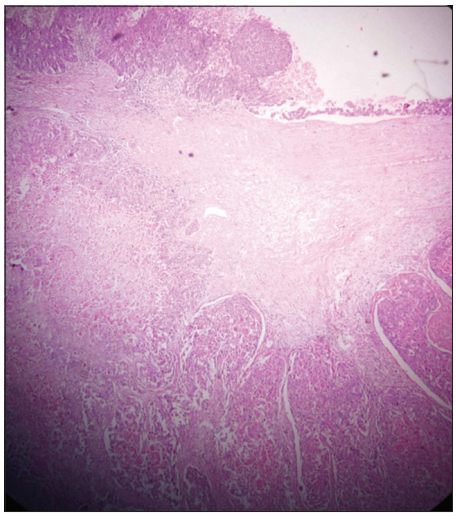

Figure 2: Hematoxylin and Eosin staining demonstrating native gallbladder mucosa lined by columnar epithelium with an abrupt transition to malignant metaplastic squamous epithelium with infiltration into muscle layer and serosa of the gallbladder (×10)

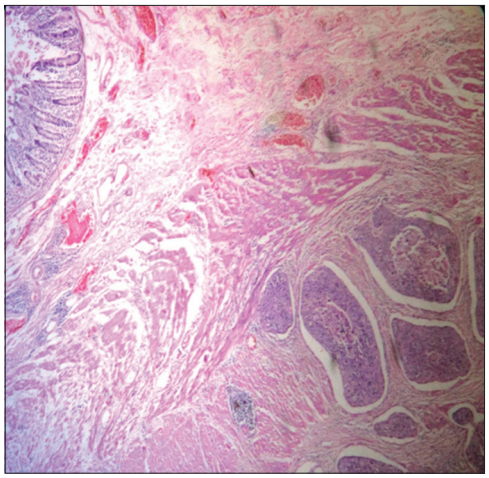

Figure 3: Infiltration of tumor into colonic wall through the serosal side (×10)

DISCUSSION

GBC is uncommon with a high fatality rate occurring over a wide geographical distribution.[9] However, it is the most common cause of death from biliary malignancies.[10] It is usually detected at an advanced stage due to its non-specific symptoms.[11] Numerous risk factors driving GBC have been implicated including demographic factors, pre-existing gallbladder disease, and environmental exposures. The definite preponderence of gallbladder carcinoma in females as found in our study stands in conformity with the elevated female GBC incidence found worldwide though the underlying causes for the same remain unknown. Endogenous estrogen and prolonged lifetime estrogen exposure have been associated with elevated risk of GBC carcinogenesis through low parity, young age at menarche, late age at first pregnancy, oral contraceptive use, estrogen replacement therapy, and prolonged fertility.[12-14] We observed a peak age incidence in the fifth to sixth decades of life. Similar results were observed in other studies from India.[15-17]

The most important risk factor for the development of GBC is gallstones, with an 8.3 times higher risk than the general population. Among patients with GBC, 70–90% have a history of cholelithiasis. Larger stones portend a greater risk, with stones >3 cm being 9.2–10.1 times greater than stones <1 cm. This increased risk is most likely attributable to greater local epithelial irritation.[9] Gallstones were present in 87.7% of our cases and the stone size ranged from 3 mm to 1.3 cm. Similar results were found by Perpetuo *et al.*[18]

Many authors have described an association between elevated CA19-9 and poor outcomes, in the setting of biliary or other malignancies, using different value cutoffs, or different measurement techniques.[19] In our study, CA19-9 levels were found to be significantly elevated in 25 patients. For the rest of the patients, the values were not available in the departmental records. In the study conducted by Ioannis Hatzaras, pre-operative CA19-9 was more predictive of survival than typical histopathological characteristics when radical resection was possible, suggesting that aggressive surgical resection still be considered even in the presence of advanced disease. In light of these findings, it is recommended that CA19-9 should be routinely measured before attempted curative resection.

CT is better at detecting lesions than the US. CT has a low sensitivity for detecting lymph node metastasis, although its positive predictive value is >90%. Both the US and CT may fail to show local gastrointestinal and omental infiltration and peritoneal deposits.[20] In our study, pre-operative imaging of the abdomen (both US and CT) showed the

presence of gallstones in 50 (87.7%) cases and tumor was detected in 49 (85.9%) cases.

Between 0.5 and 1.5% of patients who undergo a simple cholecystectomy for presumed cholelithiasis are discovered incidentally to have GBC.[21] Autopsy studies have revealed a 1–2% incidence of gallbladder carcinoma in patients with cholelithiasis.[22] Our study reveals a very high percentage of incidental gall bladder carcinoma (14%) in a relatively small sample size, which underscores the high risk of gall bladder carcinoma in our population. This signifies the importance of histopathological examination of all cholecystectomy specimens.

The most frequent histological subtypes of the malignant gallbladder tumors are the adenocarcinomas, representing approximately 90–95% of all cases. In contrast, squamous cell or "epidermoid" carcinomas and adenosquamous carcinomas are rare.[23] In our study, adenocarcinoma, not otherwise specified, constituted the most common (84.2%) histological type, with maximum (61.7%) tumors being moderately differentiated [Figure 1]. We also reported three cases of squamous cell carcinomas followed by 2 cases each of papillary and mucinous adenocarcinoma [Figure 2 and 3].

Pure squamous cell carcinoma of the gallbladder is a rare malignancy mostly described in literature as individual case reports.[24,25] In our cases, microscopic examination varied from a tumor composed of groups, islands, and nests of atypical squamous cells with dyskeratosis and keratin pearl formation to a tumor comprising of cells arranged in solid sheets with areas of comedo necrosis with infiltration into the muscle layer of gallbladder. In our study, all the cases were advanced carcinomas, with invasion beyond the muscularis. Two out of three cases were pT2 (invasion into perimuscular connective tissue) while the other one was pT3 (infiltration into adjacent liver). Lymph node metastasis was seen in two cases. All the three cases showed strong positive staining with CK 5/6 thus confirming our diagnosis. Histopathology revealed comparable findings in other studies.[26,27]

We also reported 1 case of neuroendocrine tumor in which the tumor cells were arranged in a predominantly trabecular pattern and having a mitotic count of >20/ 10 hpf which showed positive staining with chromogranin.

Staging of the patients was done according to AJCC TNM 7th edition: Stage I in 20 patients (35.1%), Stage II in 25 patients (43.9%), Stage IIIa in 10 patients (17.5%), and Stage IIIb in 2 patients (3.5.%).

In conclusion, GBC is not an uncommon clinical entity in the Kashmir valley, unlike western countries. It is mainly a disease of females in the fifth to sixth decade. Although the association between gallstones and GBC is strong, the causal relationship between them is not clear. In spite of the advanced imaging techniques, early gallbladder carcinoma is not efficiently detected. Therefore, every gallbladder should be subjected to routine histopathological examination because with the identification of an early gallbladder carcinoma a curative resection may be possible and these patients have a good long-term survival.

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