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PRIMARY GALL BLADDER CARCINOMA: A RETROSPECTIVE CLINICOPATHOLOGICAL STUDY AT A TERTIARY CARE CENTRE IN MUMBAI

Dr. Shubhangi Vinayak Agale[1]*, Dr. Sanjay Surase M D[2], Dr. Grace F. D'Costa M.D.[3], Dr. Mukund Tayade M.S.[4], Dr. Sushma Bharti[5] and Dr. Charu Sethi[6]

[1]M.D. D.C.P, Associate Professor, Department of Pathology, Grant Govt. Medical College, Mumbai-08.
[2]Assistant Professor, Department of Pathology, Grant Govt. Medical College, Mumbai-08.
[3]Professor and HOD, Department of Pathology, Grant Govt. Medical College, Mumbai-08.
[4]Professor and Head, Department of Surgery, Grant Govt. Medical College, Mumbai.
[5]Chief Resident, Department of Pathology, Grant Govt. Medical College, Mumbai.
[6]Junior Resident, Department of Pathology, Grant Govt. Medical College, Mumbai.

***Corresponding Author: Dr. Shubhangi Vinayak Agale**
M.D. (Pathology), D.C.P. Associate Professor, Department of Pathology, Grant Govt. Medical College, Mumbai-08.
Email Id:

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ABSTRACT

Aim: To establish the overall rate of gall bladder carcinoma and unsuspected (incidental) carcinoma based on our experience. **Methods:** We retrospectively evaluated all consecutive cholecystectomies performed in our institute for a period of five years in order to determine the incidence of gall bladder carcinoma and to identify common clinical and histopathological characteristics of this neoplasm. **Results:** Totally 591 cholecystectomies were performed in our institute over a period of five years. During this period the gall bladder carcinoma was diagnosed in 0.85% (5/591) of all cholecystectomy specimens. **Conclusion:** Gall bladder carcinoma is an uncommon malignancy which is commonly diagnosed incidentally in cholecystectomy specimens operated for cholelithiasis and cholecystitis.

KEYWORDS: Gall bladder carcinoma, cholecystitis, incidental gall bladder carcinoma.

INTRODUCTION

The prevalence of gall bladder carcinoma varies in different parts of the world. In the United States of America, Singapore and Nigeria, it is an uncommon malignancy with an incidence of 2.5 per 1,00,000, whereas Chile has a much higher incidence of 7.5 per 1,00,000 population.[1]

Gall bladder carcinoma is reported to be rare in Mumbai with a variation of incidence within India. The Indian Council of Medical Research Cancer Registry has recorded an incidence of 4.5 per 1,00,000 population in males and 10.1 per 1,00,000 population in females of northern parts of India and 1.2 per 1,00,000 population in females in southern parts of India.[2]

Primary gall bladder carcinoma is an uncommon entity, diagnosed in 0.3 - 1.5 % of cholecystectomies.[3-8]

This study was carried out to establish the overall rate of gall bladder carcinoma and incidental carcinoma in our institute.

MATERIALS AND METHODS

The present study was carried out at the pathology department of tertiary care centre, Mumbai; based on the evaluation of all consecutive cholecystectomies performed over a period of five years. A total of 591cholecystectomies were performed; the clinical and pathological records and slides of these cases were reviewed. From the collected data we retrieved five cases of gall bladder carcinoma of which four were incidentally detected by the pathologist. The slides were reviewed for presence of carcinoma, cholecystitis, and adjoining dysplasia. The presence of emboli and perineural invasion was noted and pathological stage was evaluated in all cases.

RESULTS

Five cases of gall bladder carcinoma were diagnosed, which comprised 0.85 % of all cholecystectomies performed. Of five cases, one case (20%) was diagnosed preoperatively and four cases (80%) were detected incidentally. So the incidence of incidentally detected gall bladder carcinoma was 0.67%.

Table No.1 shows relevant clinical and pathological data of these cases. All patients were females in the age

group of 50 - 75 years with a mean age of 60.4 years. The common presenting symptom was pain in the abdomen. The ultrasound showed cholelithiasis with cholecystitis in all five cases. Gall bladder carcinoma was diagnosed in one case on CT scan.

Pathologically, on gross examination the commonest presentation was that of a nodular lesion in the fundic region (Figure No-1a and 1b).

Microscopically adenocarcinoma (NOS) (Figure No-2) was seen in three cases and one case each of mucinous adenocarcinoma (Figure No-3) and papillary adenocarcinoma (Figure No-4). The pathological stage was pT_a and pT_3 in two cases each. In one patient, details were not known. The patients with pT_3 stage showed perineural invasion (Figure No-5) and vascular/lympahtic emboli. All the cases showed dense inflammation i.e cholecystitis. In three cases the adjacent mucosa showed dysplasia i.e carcinoma in situ (Figure 6), whereas intestinal metaplasia was seen in one case. The grade of tumour was G_1 in three cases and G_2 in two cases each.

Table 1: Clinicopathological features in cases of gall bladder carcinoma.

NO.	Age/Sex	Clinical presentation	USG/CT/MRI	Gross	Microscopy	Grade/Stage	Treatment/ Follow up
1) S/1784/05	75/F (Incidental carcinoma detected by pathologist)	Pain in abdomen	USG-S/0 chronic calculous cholecystitis.	Fundus-thickening of wall	Mucin secreting adenocarcinoma(well diff.), serosa involved. Perineural invasion++.No lymphatic emboli. Inflammation present. Adjacent mucosa-dysplasia(ca in situ)	G1/$_pT_3$	Surgery/ expired
2) S/517/07	55/F (Incidental carcinoma detected by pathologist)	Pain in abdomen	USG-Calculous cholecystitis.	Fundus-papillary nodular growth 2x1x0.5cm.Serosa UNR on gross	Papillary adenocarcinoma(well diff.), serosa spared. No lymphatic/vascular emboli. No perineural invasion. Inflammation present. Adjacent mucosa-intestinal metaplasia	G1/$_pT_{1a}$	Surgery/ No
3) S/3737/08	57/F (Incidental carcinoma detected by pathologist)	Flatulence, dyspepsia-3months. Pain in right HC-1 month	USG-Gall bladder wall thickened, gall stones ++ (10 to 12mm in size) chronic calculous cholecystitis.	Fundus-ulceration of mucosa with localized thickening of wall.	Adenocarcinoma(Mod diff.), serosa involved. Perineural/perivascular invasion++.Vascular emboli ++.Inflammation present. Adjacent mucosa-dysplasia(ca in situ)	G2/$_pT_3$	Surgery/ expired
4) S/1920/09	50/F	Pain in right HC since 4 months	USG-cholelithiasis with cholangitis. CT-GB shows generalised thickness upto 8 mm and shows a nodule 21 x 18 mm-S/O of GB carcinoma FNAC inflammatory smear-chronic cholecystitis.	-	Adenocarcinoma (well diff.), serosa involved. Other details not available.	G1/Not known	Surgery/ Lost to follow up
5) S/2205/09	65/F (Incidental carcinoma detected by pathologist)	Pain in right HC since 2 months. Acute pain in right HC – 2 days. Hypertensive. Emergency operation.	USG-cholelithiasis	Fundus-nodular growth 1.5x1.5x1 cm. Serosa grayish white.	Invasive papillary adenocarcinoma Comedo pattern(invasive component). Necosis++. Serosa notinvolved. No perineural invasion++. No lymphatic emboli. Inflammation present. Adjacent mucosa-dysplasia (ca in situ).	G2/$_pT_{1a}$	Surgery/ alive

FIGURE LEGENDS

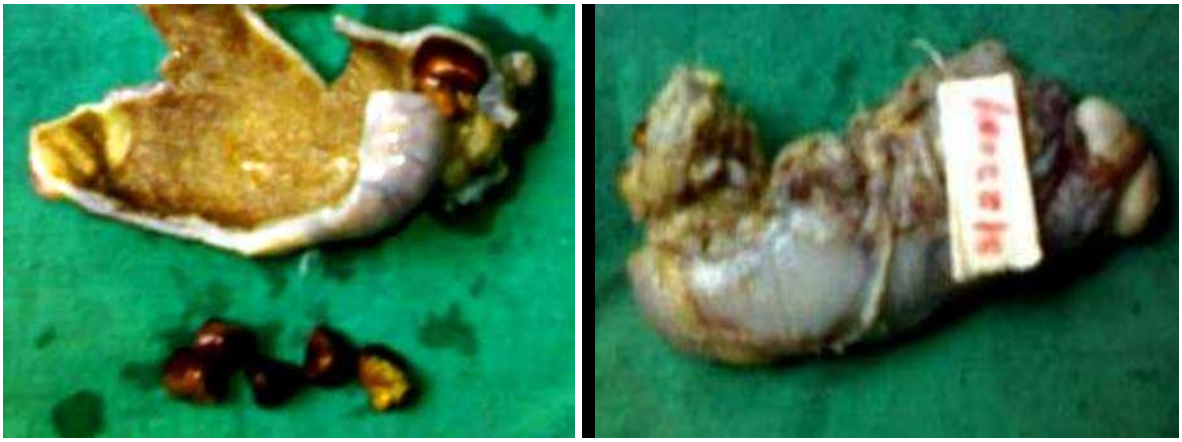

Figure 1 A & 1 B: A cholecystectomy specimen showing a grayish white growth in the fundic region and pigment stones.

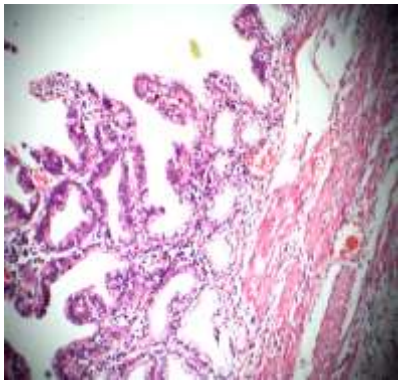

Figure 2. Adenocarcinoma of gall bladder.

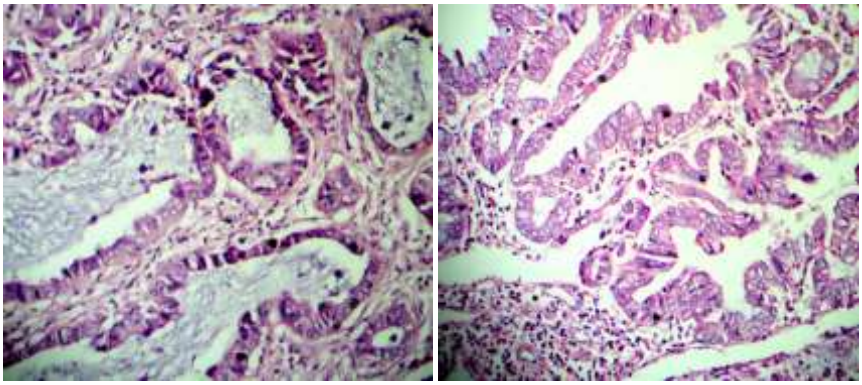

Figure 3: Photomicrograph showing mucinous adenocarcinoma (well differentiated adenocarcinoma).

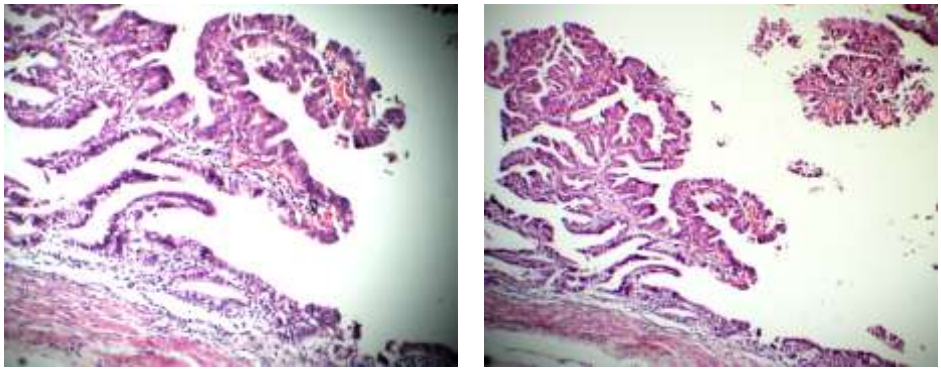

Figure 4: Photomicrograph showing papillary adenocarcinoma (moderately differentiated adenocarcinoma).

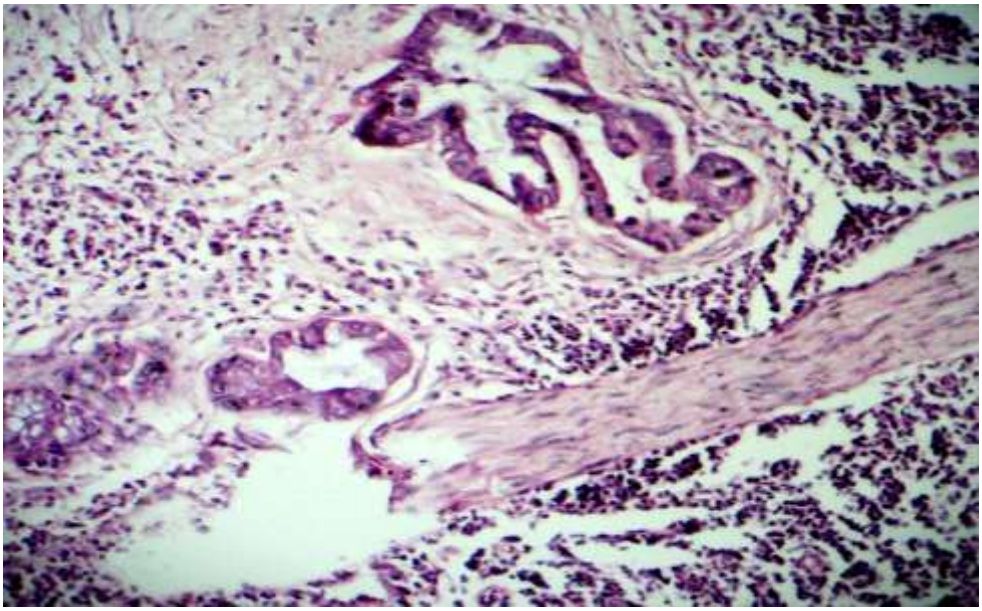

Figure 5: Photomicrograph showing perineural invasion.

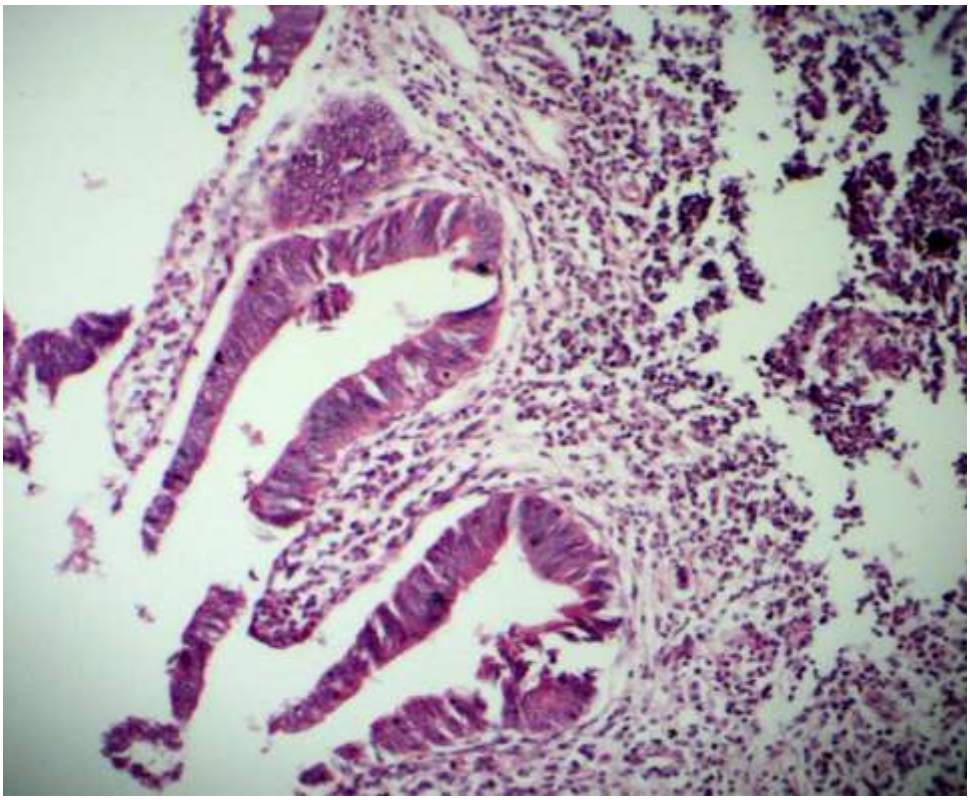

Figure 6: Photomicrograph showing carcinoma in situ.

DISCUSSION

Maxmillan Destoll is credited with the first report of gall bladder carcinoma (GBC) on the basis of two autopsies in 1777.[4] Since then, the primary carcinoma of the gall bladder has remained a uniformly fatal neoplasm. The reasons being, a) its late presentation b) early spread by lymphatic, hematogenous and direct route c) high propensity to seed the peritoneal surfaces and d) lack of effective adjuvant therapy.[5]

The etiology is unknown but there is a clear worldwide association between chronic cholelithiasis and gall bladder carcinoma. The risk of developing cancer among patients of untreated cholelithiasis has been estimated to be 0.2-0.5% over a 20 year period.[6] Among other risk factors, a number of genetic, dietary factors, endo and exobiotics, chronic inflammation and infection have been associated with the development of gall bladder carcinoma.[7]

According to Rai et al[8] higher intake of energy and carbohydrates possibly increase the risk of gall bladder carcinoma and adequate intake of fruits and vegetables probably reduce the risk of GBC as they contain potentially anticarcinogenic agents. Gallstones represent an important risk factor in the formation of gallbladder malignancies. Concrements are present in up to 85% of patients with gallbladder carcinomas.[9-15] Chronic inflammation is strongly associated with the malignant transformation of cells. Chronic inflammation causes DNA damage, which provokes repeated tissue proliferation and restoration attempts. This response involves the release of cytokines and growth factors and, thus, predisposes cells to oncogenic transformation.[15]

Chronic cholecystitis is typically caused by chronic irritation due to a cholelithiasis, which may provoke cancer development after many years.

Gall bladder carcinoma is diagnosed pathologically in 0.3-1.5% of cholecystectomy specimens. In 15-30% of cases there is no evidence of malignancy before or during operation and the disease is diagnosed microscopically, postoperatively.[9-19]

GBC is suspected preoperatively in only 30% of patients and 70% are discovered incidentally(IGBC) by the pathologist on a gallbladder specimen following cholecystectomy for benign disorders such as polyps, gallstones and cholecystitis.[14] Incidental GBC is discovered in 0.20-3% of all cholecystectomies.[14 -19]

GBC is two to six times more prevalent in women with a peak incidence in the seventh decade of life.[5] The presenting symptoms include upper abdominal pain nausea, vomiting, fever, jaundice and weight loss.[5,6]

CAES registry, which comprises 117.840 laparoscopic cholecystectomies, identified 409 (0.35%) incidental carcinomas.[19] In our series gall bladder carcinoma was diagnosed in 0.85% of cholecystectomies and 0.67% of these were incidentally detected, which is more than the results of CAES registry but currently, about two thirds of cases are an incidental finding after the removal of the gallbladder for a benign disease.[19]

All the patients were females and the mean age of diagnosis was 60.4 years (range 55-75 years). The commonest presenting symptom was pain in abdomen followed by dyspepsia.

Pathologically GBC usually presents as a mass lesion. It may however form a localized wall thickening or a polypoidal growth.[6] Approximately 60% of tumors originate in the fundus, 30% in the body and 10% in the neck.[7] On gross examination, the commonest presentation in our series, was that of a nodular lesion involving the fundus in three cases and diffuse thickening of the wall in the other two cases.

Microscopically adenocarcinomas account for 90% of GBC and they may be well moderately or poorly differentiated. There are several histological variants of adenocarcinoma i.e. papillary, intestinal, mucinous, signet ring cell and clear cell. In our study, histologically, all the cases were diagnosed as adenocarcinomas; 3 cases were well differentiated adenocarcinomas [2 cases of adenocarcinoma (NOS) and a single case of mucinous adenocarcinoma] and 2 cases were moderately differentiated adenocarcinomas [single case each of adenocarcinoma (NOS) and papillary adenocarcinoma].

The main prognostic factors for gall bladder carcinoma are the clinical and pathological stage. The size of the tumor, its location in the gall bladder, presence or absence of dysplastic mucosa and grade of the tumor are some of the other important factors that guide surgical options and predict outcome.[6]

The overall outcome of this disease is dismal with the 5 year survival rate being less than 5% with a median survival of 5 to 8 months.[5-14]

Adjuvant chemotherapy and or radiotherapy for patients with GBC has not altered the dismal prognosis.[5-19] The prognosis of an incidental carcinoma, although better than preoperative suspected one, it is still modest: reported survivals at 5 years in the literature are, respectively, 35% vs. 5%, with a median of 26.5 vs. 9.2 months in suspected cases.[19]

CONCLUSION

In conclusion, the incidental carcinoma of gallbladder, comprises of nearly 80% of all gall bladder carcimomas in this study. So we would like to recommend that all cholecystectomy specimens should be submitted to pathology laboratory, as incidental gall bladder cancinoma can be detected only by histopathological examination. It is important to carry out careful and detailed gross as well as microscopic examination of every gall bladder specimen irrespective of clinical diagnosis, so that we can detect true incidence of gall bladder carcinoma.

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