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CASE REPORT

LARGEST REPORTED CASE OF CARCINOMATOUS GALLBLADDER ASSOCIATED WITH INTRA CHOLECYSTIC PAPILLARY NEOPLASM (ICPN) WITH BRIEF REVIEW OF LITERATURE

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ABSTRACT: Gallbladder carcinoma is the most common cancer of the biliary tract and the fifth most common neoplasm of the digestive tract. The majority of symptomatic malignant gallbladders are inoperable. Although any chronic pathology obstructing the biliary outflow can result in an enlarged gall bladder, an intrinsic gall bladder malignancy producing a giant gallbladder is unusual. A woman in her 40 s presented with complaints of a progressive abdominal lump of 2 years duration, which was thought to be an ovarian mass. After evaluation, the patient was found to have a giant gallbladder secondary to Intra cholecystic papillary neoplasm associated with invasive carcinoma. Given the rarity of a giant gallbladder, the combination of both giant gallbladder and symptomatic operable carcinomatous gallbladder is even rarer. There are only 3 reported cases of carcinomatous giant gallbladder, 2 of which are operable. We present one such case.

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Impact statement: Giant gallbladder is a rare finding and association with carcinoma is even rarer. This article describes this unique case scenario with a summary of published scarce literature thus far and a brief review on intra cholecystic papillary neoplasm associated carcinomas.

Key words: *carcinoma gallbladder, ICPN, giant gallbladder, gallbladder malignancy, surgical oncology.*

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INTRODUCTION

Gallbladder carcinoma is the most common cancer of the biliary tract and the fifth most common neoplasm of the digestive tract. The overall incidence is 3 per 100000 people. It is diagnosed preoperatively only in 30% of cases, with the remaining 70% of cases diagnosed postoperatively after cholecystectomies for benign indications. The majority of symptomatic malignant gallbladders are inoperable. The overall 5-year survival rate is less than 5% (1). Although any chronic pathology obstructing the biliary outflow can result in an enlarged gall bladder, an intrinsic gall bladder malignancy producing a giant gall bladder is unusual.

Though there is no standard definition, gallbladders of size >14 cm or volume >1.5 liters (similar to or larger than an adult liver) have been regarded as Giant Gallbladders (2). Given the rarity of a giant gallbladder, the combination of both giant gallbladder and symptomatic operable carcinomatous gallbladder is even rarer. There are only 3 reported cases of carcinomatous giant gallbladder, 2 of which are operable. We present one such case.

CASE PRESENTATION

A woman in her fourth decade of life presented with complaints of a progressive abdominal lump of 2 years duration associated with intermittent dull aching pain for five months. History of loss of appetite and unquantified weight loss were present. There was no significant medical or surgical history except for tubectomy.

On examination, she was anicteric, with a performance status of ECOG 2. The abdomen was asymmetric due to the lump on the right side, extending from the right hypochondriac region superiorly to the right iliac region inferiorly. Palpation revealed a solitary, globular, firm gall bladder lump of 26 x 10 cm.

Complete hemogram, liver function tests, and coagulation profile were within normal limits. Serum Carbohydrate antigen 19-9 (CA 19.9) was 0.8 units/mL (normal 0-37 units/mL). Serum Carcinoembryonic antigen (CEA) was 4.3 ng/mL (normal 1-5 ng/mL). The magnetic resonance imaging (MRI) done was suggestive of an overdistended gallbladder measuring 21.5 x 9.5 x 10.4 cm (CC x AP X Transverse) extending up to the anterior abdominal wall and causing thinning due to mass effect. Multiple altered signal intensity polypoid-like lesions, which are heterogeneously hypointense on T2 and STIR (Short Time Inversion Recovery), iso to hyperintense on T1, with evidence of restricted diffusion on DWI (Diffusion Weight Imaging) noted arising from the walls of gall bladder (GB) predominantly in the neck region. The findings were suggestive of neoplastic etiology (**Figure 1A**, **B**, **C**, **D**).

The case was taken up for surgery after a discussion at the Multi-Disciplinary Tumor Board meeting (MDTB). Intraoperatively, there was no evidence of serosal involvement. There is no evidence of liver metastasis, peritoneal or omental deposits, or free fluid in the peritoneal cavity. There were no enlarged nodes and fat planes with surrounding structures were well maintained. On palpation, the disease was creeping into the cystic duct. The cholecystectomy was done along with a wedge resection of the gallbladder fossa with a 2 cm rim of non-neoplastic liver tissue. The common hepatic duct was excised from a distance of 2 cm from the confluence with the cystic duct till the retro pancreatic portion of the bile duct. Portal lymphadenectomy was carried out. Biliary continuity was restored with hepaticojejunal anastomosis (**Figure 2A**, **B**, **C**). Microscopically, the lesion was a well differentiated intracystic papillary neoplasm with associated invasive carcinoma (adenocarcinoma, intestinal

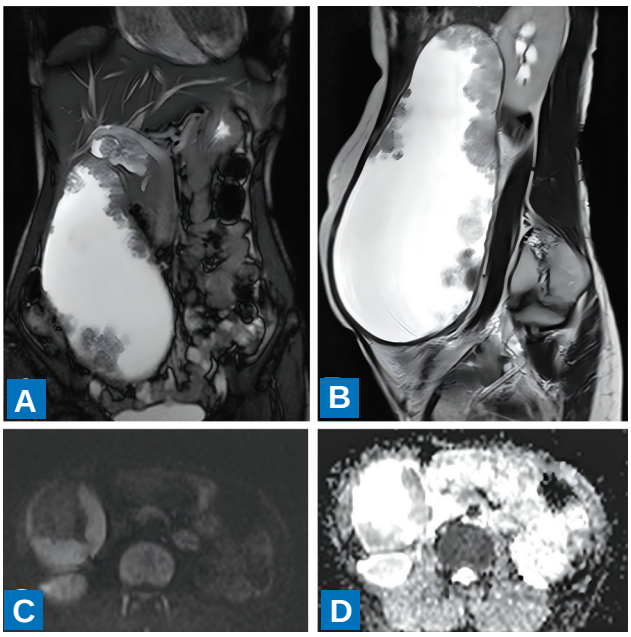

Figure 1. *MRI images. (**A**) Coronal; (**B**) sagittal T2 weighted images showing hypointense lesion in the gall bladder; (**C**) diffusion-weighted imaging (DWI); (**D**) apparent diffusion coefficient (ADC) imaging, demonstrating the lesion arising from the walls of gallbladder predominantly in the neck and body region with restricted diffusion on DWI.*

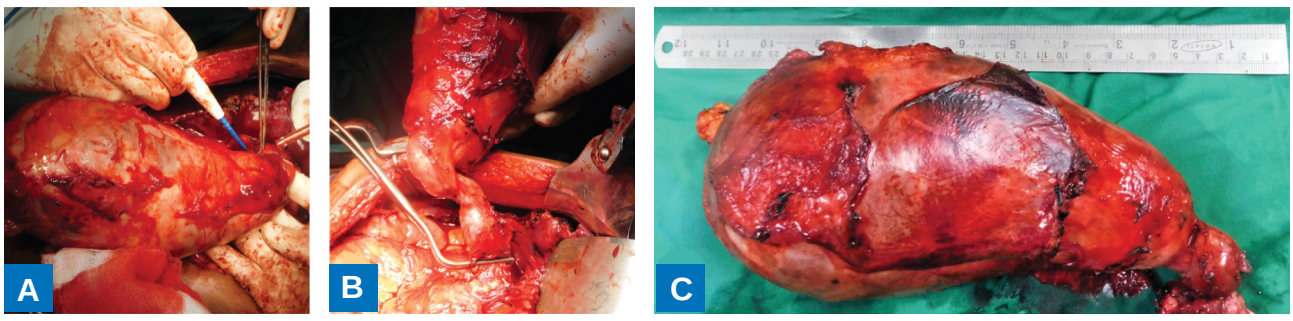

Figure 2. *Preoperative and intra operative clinical images. (**A**) Intra operative image of the gallbladder; (**B**) intra operative image showing dilated cystic duct; (**C**) resected gallbladder specimen (measuring scale for reference).*

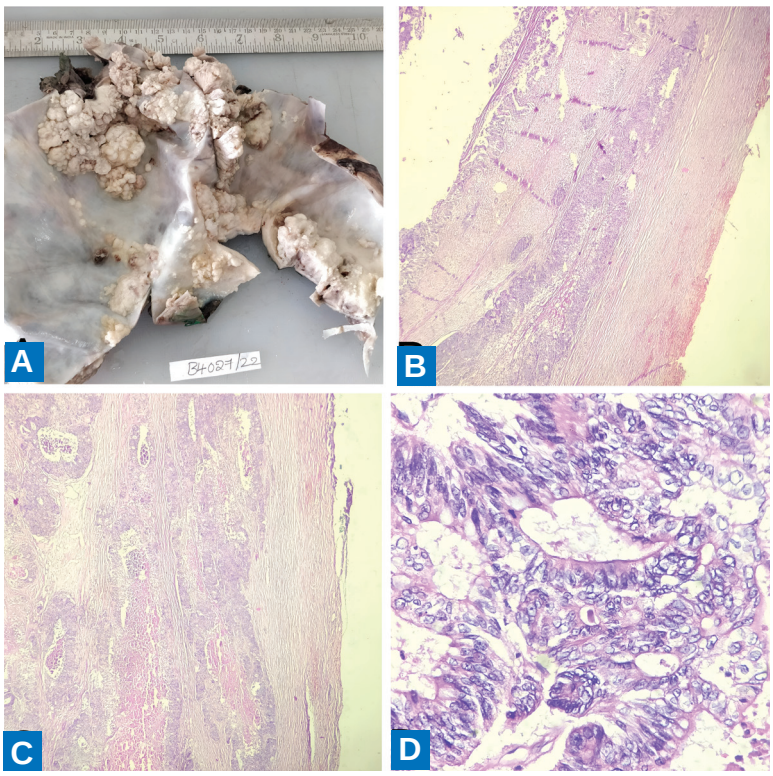

Figure 3. *Pathological evaluation of the resected specimen. (**A**) Cut section of the gall bladder showing a polypoidal lesion; (**B, C**) H and E sections from the gall bladder showing an infiltrative lesion extending into the peri muscular connective tissue on the peritoneal side without serosal involvement (original magnification X100); (**D**) H and E sections showing the lesion arranged in papillae. The neoplastic cells are columnar with pleomorphic vesicular nuclei, some with prominent nucleoli, moderate amount of eosinophilic cytoplasm (original magnification X400).*

type) invading the peri muscular connective tissue on the hepatic aspect with no extension into the liver (**Figure 3A**, **B**, **C**, **D**). All margins (common hepatic and cystic duct margins) are negative for invasive carcinoma. No nodal involvement. Stage II (pT2b N0). Post-surgery, three cycles of gemcitabine (GEM) plus cisplatin (CDDP) combination adjuvant therapy was given. She defaulted for 1 year and presented with metastatic disease. She is currently undergoing adjuvant therapy in the form of capecitabine plus oxaliplatin (CapeOX).

DISCUSSION

The terminology for precursor lesions of the digestive system was standardized in the 2019 World Health Organization (WHO) classification. The term 'intra-epithelial neoplasia' is selectively used for pancreas, gallbladder, and biliary tree lesions whereas 'dysplasia' is used for the tubal gut. The term 'carcinoma *in situ*' (Latin for 'in its place') refers to abnormal cells that are in their place and leads to confusion when used to denote lesions that have an exophytic growth pattern. Moreover, papillary in situ carcinomas have traditionally been grouped along with invasive adenocarcinoma under the 'papillary adenocarcinomas' category. Therefore, it is not recommended. The inclusion of preinvasive lesions that have an exophytic growth pattern (≥1 cm), exhibiting a specific cellular lineage, with varying degrees of dysplasia and growth patterns into a single category is practical, especially when it has a clinical significance. Hence
'intra-epithelial neoplasia' is a new concept selectively used for pancreas, gallbladder, and biliary tree lesions. This term is used for preinvasive neoplastic lesions. The term 'carcinoma in situ' is not recommended because of its ambiguity. Intra cholecystic papillary neoplasm (ICPN) is categorized as a separate entity per the 5th edition of the WHO classification of digestive system tumors (2019). Intraductal papillary neoplasm of the bile duct (IPNB) and Intraductal papillary mucinous neoplasm of the pancreas (IPMN) are counterparts of ICPN, which are precursors of cholangiocarcinoma and pancreatic duct adenocarcinoma respectively. Another significant change is replacing the three-tiered grading system with a two-tiered system (low- versus high-grade) in the pancreaticobiliary system (3).

ICPN is defined as gallbladder lesions of intraductal papillary neoplasms of the bile duct. (4) IPNB is defined as biliary tumors with an exophytic nature exhibiting papillary mass, which can be detected macroscopically within the bile duct lumen and is characterized by intraluminal growth (5). ICPN and IPNB have similar histopathological characteristics. ICPN is classified further into four morphological subtypes: biliary (most common), gastric, intestinal, and oncocytic, based on the differences in mucus glycoprotein expression. More than 50% of ICPNs are associated with invasive carcinoma at the time of diagnosis, but only 6.4% of all invasive gall bladder carcinomas are associated with an ICPN component (4).

There is no established image-based malignancy stratification system for ICPN. As ICPN associated carcinomas have better outcomes, pre-operative identification aids in prognostication. Polypoid lesions, Increased gallbladder wall thickness, especially at the base of the polypoidal lesions, irregular borders, discontinuous mucosa, peri cholecystic infiltration, and absence of gall stones are the features associated with invasive carcinoma in ICPN (6).

The prognosis for ICPNs is considerably better than for other invasive GB carcinomas. The prog-

Table 1. *Case reports of giant gallbladders reported till date.*

S. NO.	PUBLICATION	PMID	AGE	SEX	GB SIZE (CM)	GB VOLUME	PATHOLOGY
1	Petit, before 1750 (8)	NA	27-28	F	NR	2 pintes (2 L)	NR
2	Van Swieten, 1754 (9)	NA	12	M	NR	8 libras (2.6 L)	NR
3	Collinson (10)	NA	NR	NR	NR	12.5 L	NR
4	Neudörfer, 1911 (10)	NA	50	F	NR	5.25 L	NR
5	Kehr, 1913 (10)	NA	NR	NR	NR	1.5 L	NR
6	Grosberg, 1962 (11)	13950734	95	F	14 x 5.5 cm	NR	Acute gangrenous cholecystitis, cholelithiasis
7	Maeda *et al.*, 1979 (12)	527798	36	F	18 x 4 cm	NR	Chronic cholecystitis, cholelithiasis
8	Borodach *et al.*, 2005 (13)	33726732	67	F	20 x 12 cm	1.5L	
9	Hsu *et al.*, 2011 (14)	21217498	87	F	16.4 x 13.6 x 7.8 cm	NR	Acute cholecystitis, gallbladder adenocarcinoma
10	Panaro *et al.*, 2012 (15)	22353353	17	NR	43 x 21 cm	2.7 L	PFIC-2
11	Zong *et al.*, 2013 (16)	23255925	55	F	30 x 18 cm	4 L	Congenital Hydrops
12	Chapman et al., 2014 (17)	25262725	59	F	18 cm	NR	Gallbladder adenocarcinoma with liver metastasis
13	Kuznetsov *et al.*, 2014 (18)	25194602	77	F	17.2 x 16.1 x 24 cm	3.35 L	Chronic cholecystitis
14	Yadav *et al.*, 2017 (19)	28315816	46	F	30 cm	NR	Chronic cholecystitis with mucocele
15	Fultang *et al.*, 2019 (2)	31695995	63	F	19.5 x 5.4 x 5.6 cm	NR	Chronic cholecystitis with cholelithiasis
16	Bains, Maranna *et al.*, 2020 (20)	33726732	65	F	24 x 9 cm	NR	Adenocarcinoma of gallbladder
17	Jahantab *et al.*, 2020 (21)	32884849	36	F	22 x 6 cm	NR	Gangrenous cholecystitis
18	Present case		40	F	21.5 x 9.5 x 10.4 cm	NR	Adenocarcinoma with intracystic papillary neoplasm

GB: Gallbladder; F: Female; M: Male; NR: Not Recorded; PFIC: Progressive Familial Intrahepatic Cholestasis; PMID: PubMed Identifier; NA: Not Applicable (Unpublished Manuscripts).

nosis for non-invasive ICPNs is significantly better, as seen by the 90% and 78% 3- and 5-year survival rates compared to 60% and 60% for invasive ICPNs (4). Even when associated with carcinoma, a gall bladder carcinoma with an ICPN component has a better prognosis than one without (7).

Despite the enormous size of the GB, the slow growth and non-invasive nature of ICPN have made surgery possible in this case. This contrasts invasive carcinomas, which advance locally and metastasize early before becoming symptomatic, rendering them inoperable. Hence, symptomatic operable GB malignancy is very rare. The depth of invasion is the prime determinant of the prognosis, irrespective of the size, as proved in our case. Although no randomized trials compare simple *vs*. radical cholecystectomy, the available retrospective studies demonstrate a better overall survival after a radical cholecystectomy, which is currently the standard of care. There is no standard definition for a giant gall bladder. Gallbladders of size >14 cm or volume >1.5 liters (similar to or larger than an adult liver) have been regarded as Giant Gallbladders (2). We found only a few cases of giant gallbladder reported after searching PubMed and Cochrane databases. The early recorded cases before the 1950s were from unpublished manuscripts and lacked complete details (**Table 1**). Surprisingly, all the cases reported were female patients. Most of them were a result of benign pathologies. Only three of these reported cases were malignant; our case is the largest reported case of carcinomatous giant gallbladder to date.

CONCLUSIONS

Symptomatic gallbladder carcinoma is usually inoperable. If found operable, always consider ICPN as a differential diagnosis.

More than 50% of ICPNs are associated with invasive carcinoma at the time of diagnosis, but only 6.4% of all gallbladders invasive carcinomas are associated with an ICPN component.

Polypoid lesions, Increased gallbladder wall thickness, especially at the base of the polypoidal lesions, irregular borders, discontinuous mucosa, peri-cholecystic infiltration, and absence of gall stones are the features associated with invasive carcinoma in ICPN.

Even when associated with carcinoma, a gallbladder carcinoma with an ICPN component has a better prognosis than one without.

COMPLIANCE WITH ETHICAL STANDARDS

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Conflict of interests

The Authors have declared no conflict of interests.

Availability of data and materials

The data underlying this article are available within it.

Authors' contributions

HN, SNK and NY were the responsible surgeons on whom the patient management, day to day patient care and follow up rested. NY and HN wrote the first draft of the manuscript. HN and SNK provided insight and valuable inputs to the manuscript.

Ethical approval

Human studies and subjects

The informed consent has been obtained from the patient and is in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

Animal studies

N/A.

Publication ethics

Plagiarism

Authors declare no potentially overlapping publications with the content of this manuscript and all original studies are cited as appropriate. This topic was presented at the joint conference of Indian society of Medical and Pediatric Oncology (ISMPO) and Indian Society of Oncology (ISO) held in October 2022 at Chennai, India. This manuscript has not been published nor is it under consideration for publication elsewhere.

Data falsification and fabrication

All the data corresponds to the real.

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