

Gallbladder Carcinoma Masquerading as Calculous Cholecystitis: A Rare Case Report

RANJANI MOHAN¹, PRIAVADHANA RAJAN PRASAAD², MEENAKSHISUNDARAM KUMARESAN³



ABSTRACT

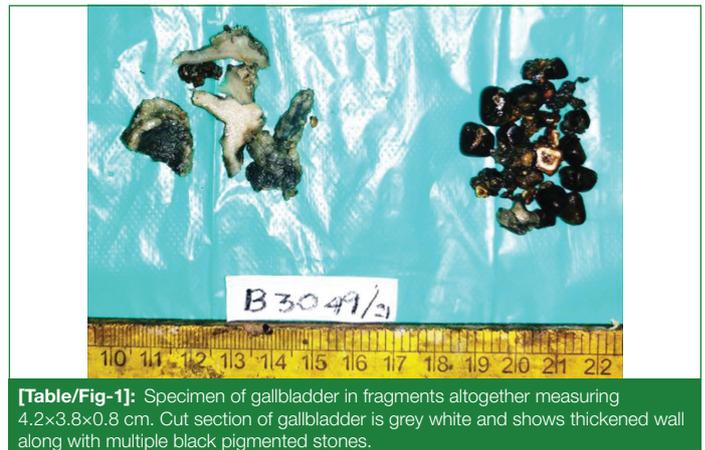
The incidence of Gallbladder carcinomas are very rare and may go undetected in radiology. Gallbladder carcinomas account for 1.2% of cancers globally. Gallbladder is the commonest site of cancers of biliary tract and most are adenocarcinomas arising from secretory cells. Most patients are females in their fourth and fifth decades, presenting with vague symptoms like pain and discomfort in locally advanced disease. Most are diagnosed in cholecystectomies done for calculi, polyp or cholecystitis. Biliary type of adenocarcinoma is the most common histologic subtype reported in the literature. The signet ring cell carcinoma of gallbladder is an uncommon subtype with very few reported cases in the past. Here authors report a case of signet ring cell carcinoma of gallbladder in a 42-year-old female patient who presented with dull aching pain in right hypochondrium for six months. Ultrasound and Computed Tomography (CT) revealed calculous cholecystitis with pericholecystic fluid collection. But the final histopathology revealed an unusual variant of gallbladder carcinoma.

Keywords: Gallbladder cancer, Immunohistochemistry, Signet ring cell carcinoma

CASE REPORT

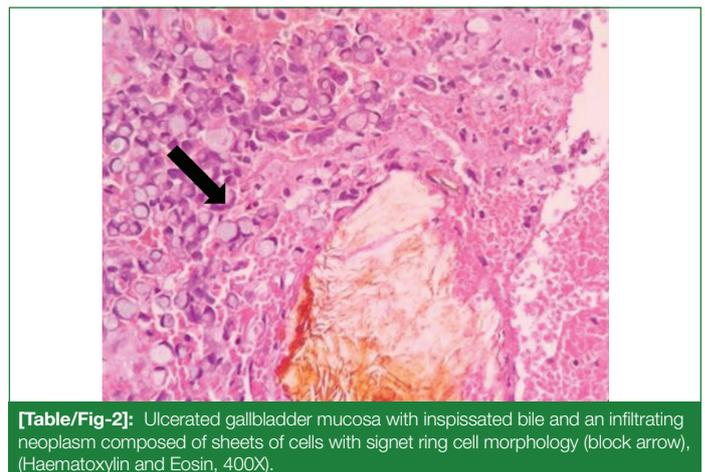
A 42-year-old female reported with fullness and dull aching pain in the right hypochondrium for a duration of six months. The patient noted the pain was periodic and it aggravated following a meal. The patient's past medical history was insignificant with no major co-morbidities. Obstetric history of two normal vaginal deliveries with last child birth 16 years ago. Preliminary upper gastrointestinal endoscopy showed the findings of oesophagitis and antral gastritis. Ultrasound abdomen revealed features of contracted gallbladder with multiple calculi of size ranging from 3-8 mm. Also noted was fluid collection of size 4.6x3.6 cm adjacent to gallbladder fossa (? Perforation). CT of the patient revealed partially distended gallbladder with multiple radiodense calculi largest measuring 8.9x4.7 mm and thick oedematous wall (maximum wall thickness ~6.8 mm). A well-defined loculated peripherally enhancing thin-walled cystic area/collection was noted in the pericholecystic region in between gallbladder and the pylorus of the stomach measuring 5.3x4.8x4.6 cm. An impression of calculous cholecystitis with loculated collection in pericholecystic region in CT was given. With a provisional diagnosis of calculous cholecystitis with pericholic abscess, surgery was performed. Intraoperatively, laparoscopic removal of gallbladder was difficult as the gallbladder was adherent to the inferior portion of liver. Gallbladder was removed in fragments and the specimen was sent to the pathology department. Grossly received gallbladder in multiple fragments aggregate measuring 4.2x3.8x0.8 cm along with multiple blackish stones aggregate measuring 4x3x0.5 cm. Gallbladder mucosa was irregularly thickened and gallbladder wall thickness was 0.5-1 cms [Table/Fig-1]. Specimen was processed routinely and submitted for histopathological examination.

Microscopic sections revealed gallbladder mucosa with an infiltrating neoplasm composed of pleomorphic malignant epithelial cells arranged in sheets and focally in glandular pattern [Table/Fig-2]. Lymphovascular and perineural invasion was seen [Table/Fig-3,4]. Numerous signet ring cells with abundant clear cytoplasm and peripherally pushed nucleus was also seen. Tumour was extending upto the serosa. Histopathological diagnosis of gallbladder adenocarcinoma was made. Since, the incidence of primary

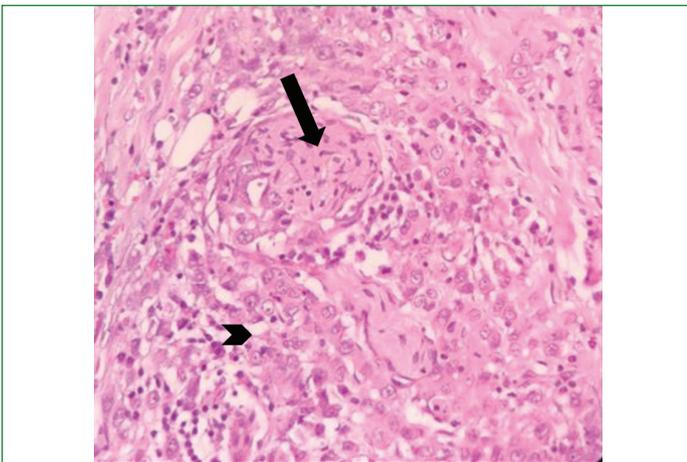


[Table/Fig-1]: Specimen of gallbladder in fragments altogether measuring 4.2x3.8x0.8 cm. Cut section of gallbladder is grey white and shows thickened wall along with multiple black pigmented stones.

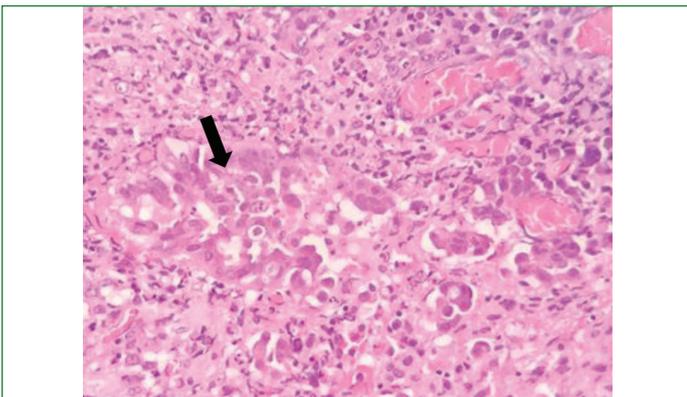
gallbladder carcinoma, signet ring cell variant is low, to rule out metastatic signet ring cell carcinoma arising from stomach and colon immunohistochemistry was performed. The panel included CK7, Carcinoembryonic Antigen (CEA) and Epithelial Membrane Antigen (EMA) for gallbladder adenocarcinoma, Hep Par1 for Hepatocellular carcinoma, P63 for metastatic squamous cell carcinoma, CK20 for colonic and pancreatic metastatic adenocarcinomas.



[Table/Fig-2]: Ulcerated gallbladder mucosa with inspissated bile and an infiltrating neoplasm composed of sheets of cells with signet ring cell morphology (block arrow), (Haematoxylin and Eosin, 400X).

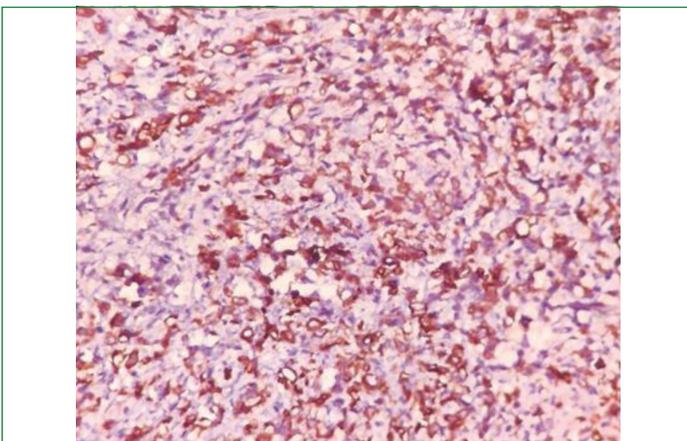


[Table/Fig-3]: Perineural invasion. Arrow highlights Nerve bundle; Arrowhead highlights tumour cells (Haematoxylin and Eosin, 400X).



[Table/Fig-4]: Angioinvasion within the gallbladder wall (Block arrow shows vessel with lumen showing tumour embolus) (Haematoxylin and Eosin, 400X).

Immunohistochemical studies showed the tumour cells to be positive for CK7 [Table/Fig-5], CEA and EMA. The tumour cells were negative for HepPar1, p63 and CK20.



[Table/Fig-5]: Strong positivity for CK7 in the tumour cells, 400X.

Hence, a diagnosis of signet ring cell variant of adenocarcinoma of gallbladder was given. As the specimen was received in fragments the surgical resection margin of cystic duct could not be commented upon for a revised surgery. The patient has undergone 10 cycles of chemotherapy initially with gemcitabine and cisplatin and later with FOLFIRI regimen (Folinic acid, Fluorouracil and Irinotecan hydrochloride).

DISCUSSION

Gallbladder carcinomas are low incident neoplasms contributing for 1.2% of global cancer diagnosis and 1.7% of global cancer deaths [1]. Risk factors for gallbladder carcinoma includes chronic inflammation due to bacterial infection or calculous cholecystitis, gallbladder polyps and anomalous junction of pancreatico-biliary

duct. Early stage carcinomas have a good overall 5-year survival of 75% with advanced stages having a 5-year overall survival of less than 5% [2]. Most patients are asymptomatic until the advanced stage. Females in the 4th and 5th decade are most commonly affected. Adenocarcinoma of the gallbladder has many histological subtypes namely biliary, intestinal, gastric foveolar, mucinous, signet ring cell, clear cell, cribriform, adenosquamous, squamous, hepatoid, carcinosarcoma and undifferentiated. More common histologic types of adenocarcinoma are the intestinal type, the clear cell and mucinous types. The signet ring cell carcinoma is a rare histologic variant. Signet ring cell variant is diagnosed when more than 50% of the tumour population is composed of signet ring cells [3,4]. Signet ring cell variant of gallbladder carcinoma was also reported by Al Khader A et al., [5], Ahamed Z and Qureshi A [6], Karabulut Z et al., [3] and Mondal K and Mandal R, [7]. Ahmad Z and Qureshi A, reported a similar signet ring cell variant of gallbladder carcinoma in a 53-year-old woman. The authors used immunohistochemical markers CK (AE1/AE3), CK7, CK20 and CDX2 to differentiate from metastatic signet ring cell carcinoma [6]. Karabulut Z et al., reported a similar case in a 76-year-old male patient who succumbed to disease in spite of radical surgery and chemotherapy in three months [3]. Mondal K and Mandal R, recorded a similar case in a 43-year-old female operated for calculous cholecystitis, specimen's resection margin showed tumoural deposits hence patient underwent radical cholecystectomy with removal of subxiphoid port, gallbladder fossa and the cystic stump. The case reported a recurrence free survival of five months [7]. The possibility of metastatic signet ring cell carcinoma from other sites should be ruled out using immunohistochemistry before making a diagnosis of primary gallbladder signet ring cell carcinoma. Gastric signet ring cell carcinoma is positive for CK7, CK20 and MUC2 and negative for MUC1. Signet ring cell carcinoma of the breast are CK7 negative, MUC1 negative, CK20 negative and are Estrogen Receptor Positive. Colonic signet ring cell carcinoma are usually CK20 and MUC2 positive and CK7 and MUC1 negative. In present case, the tumour was positive for CK7 and negative for CK20, thus confirming gallbladder carcinoma and ruling out metastasis [8]. A keen eye on the diagnostic pitfall of benign metaplastic signet ring cells should also be considered which exhibits E-Cadherin but no p53 mutation [9]. The current practices in management of gallbladder cancer involves radical cholecystectomy for stage Ib (tumour invading muscle layer) tumours, Radical En Bloc Resection including liver bed in stage II tumours (tumour invading perimuscular connective tissue), radical resection selectively in some patients with stage III tumours (tumour perforating serosa or directly invading liver) and stage IV tumours are generally unresectable. Tis (confined to mucosa) and T1a (confined to lamina propria) tumours are cured by simple cholecystectomy [10]. Chemotherapy for locally advanced disease includes gemcitabine and cisplatin in the first line and other drugs include fluorouracil and irinotecan. The FOLFIRI regimen as first line or as second line post gemcitabine and cisplatin regimen gave a progression free survival of 2.4-3 months [11]. The patients with more than T2 stage, patients with node positive status also benefitted from targeted radiotherapy [12]. Better treatment strategy is needed to treat the patients of gallbladder carcinoma.

CONCLUSION(S)

The case report signifies the importance of submitting all calculous cholecystitis specimen for histopathologic examination. Signet ring cell variant of gallbladder carcinoma is a rare histologic subtype of adenocarcinoma. However, the differential diagnosis must include metastatic signet ring cell carcinoma from stomach, colon, prostate, bladder or breast. Immunohistochemical markers CK7, CK20, CEA, EMA play an important role in differentiating them. Although this histologic variant is associated with poor prognosis, if these tumours are picked up in early stages a more detailed surgical resection can be curative for the patient.

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PARTICULARS OF CONTRIBUTORS:

1. Assistant Professor, Department of Pathology, ESIC Medical College and PGIMS, Chennai, Tamil Nadu, India.
2. Assistant Professor, Department of Pathology, ESIC Medical College and PGIMS, Chennai, Tamil Nadu, India.
3. Professor and Head, Department of Pathology, ESIC Medical College and PGIMS, Chennai, Tamil Nadu, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Ranjani Mohan,
Assistant Professor, Department of Pathology, ESIC Medical College, K.K. Nagar,
Chennai, Tamil Nadu, India.
E-mail: drranjanimohan@gmail.com

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