Case Report

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Pathology Section

Gall Bladder Carcinoma: A Case of Clear Cell Variant

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ABSTRACT

Gall Bladder Carcinoma (GBC) is the fifth most common malignancy of the gastrointestinal tract and the most common malignancy of the extrahepatic biliary tract. The most frequent sites of occurrence are in the fundus, body, and neck. The overall incidence is approximately three per 100,000 people, varying depending on geography and ethnicity. The occurrence of the clear cell variant is rare, while adenocarcinoma is the most common occurring subtype. This form was first recognised by Albores-Saavedra and Henson. The incidence of GBC varies due to geographic and ethnic differences. The majority of cases are usually diagnosed incidentally after cholecystectomy or at an advanced stage. The authors present a case of a 40-year-old female who presented to the tertiary care center with a classical complaint of chronic cholecystitis for one month, accompanied by elevated total bilirubin and mildly elevated alkaline phosphatase. Radiological investigations revealed a mildly distended Gall Bladder (GB), thickening of the wall of the fundus, and multiple small calculi. After undergoing cholecystectomy, a histopathological examination revealed adenocarcinoma with a clear cell type, characterised by tumour cells arranged in nests with abundant clear cytoplasm. This led to a provisional diagnosis of GBC clear cell variant. The diagnosis was then confirmed by immunohistochemical stains. The clear cell carcinoma variant of the gall bladder is rare, and not much has been reported about it. It is important to differentiate between a primary and a metastatic tumour, with the possibility of clear cell renal carcinoma metastasis being one concern. This differentiation is crucial to avoid misdiagnosis and prevent delays in appropriate therapy.

Keywords: Adenocarcinoma, Cholecystectomy, Cholecystitis, Gallstone, Renal cell carcinoma

CASE REPORT

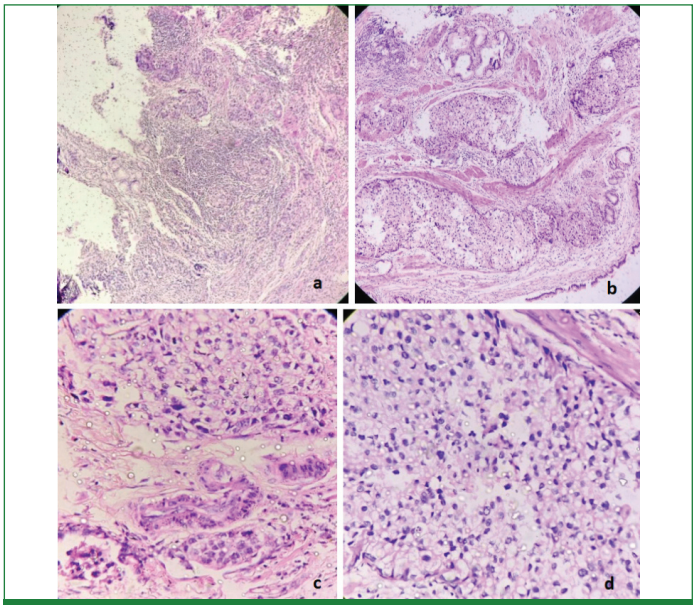
The authors present a case of a 40-year-old female who was presented to the Surgery Outpatient Department with classical complaints of chronic cholecystitis, characterised by non-radiating pain localised in the Right Upper Quadrant (RUQ) region, nausea and vomiting, loss of appetite, and jaundice for one month. She had no history of fever, weight loss, lymphadenopathy, or any pre-existing co-morbidities.

Liver function tests (LFT) showed elevated total bilirubin (5.5 mg/dL) (reference range: 0.1-1.2 mg/dL) and mildly elevated alkaline phosphatase (145 U/L) (reference range: 44-147 U/L), with normal alanine aminotransferases and aspartate aminotransferases. A Complete Blood Count (CBC) showed mild leucocytosis, with a total leukocyte count of 14,700/cmm (reference range: 4,000-11,000/cmm).

Ultrasonography (USG) of the abdomen revealed a mildly distended gall bladder and thickening of the wall of the fundus, along with multiple small calculi, the largest measuring 2.3×1.4 mm. Furthermore, Magnetic Resonance Cholangiopancreatography (MRCP) was also performed, which revealed asymmetrical thickening of the fundus and dilated intrahepatic biliary radicals, along with a mildly dilated Common Bile Duct (CBD). Multiple calculi were noted, the largest measuring 2.5×1.5 mm.

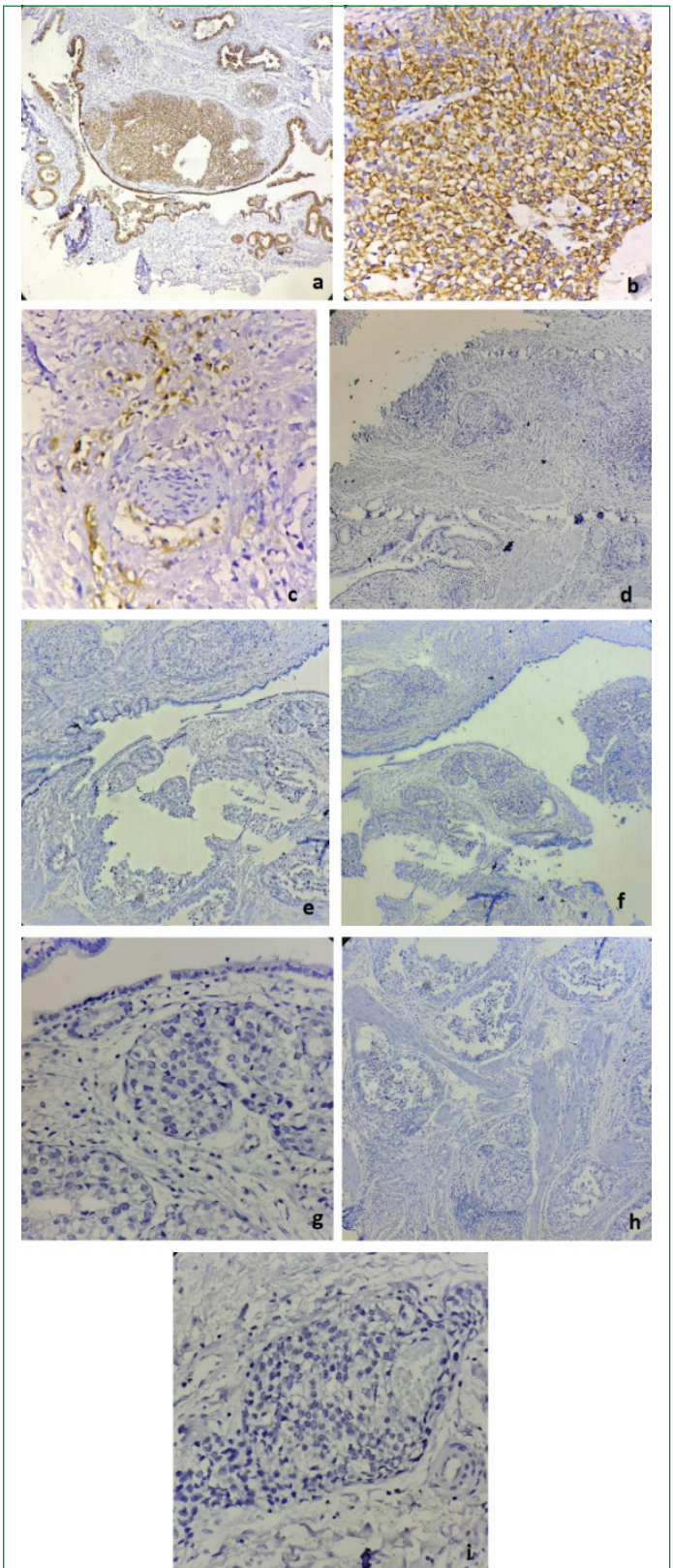
The imaging studies were not available, as we collected the data from hospital records. The patient underwent cholecystectomy along with CBD exploration. The specimen was then sent for histopathological examination. Grossly, the gall bladder measured 6×3×1.5 cm. Upon opening the gall bladder, multiple pigment stones were identified, and a growth near the fundus measuring 2×1×1 cm was noted.

Microscopic examinations revealed adenocarcinoma with the clear cell type, characterised by tumour cells arranged in nests, having abundant clear cytoplasm, distinct borders, and large hyperchromatic nuclei with mild atypia and occasionally prominent nucleoli. The tumour exhibited invasion into the liver, cystic duct margin, neck margin, and liver parenchyma margin [Table/Fig-1a-d]. Lymphovascular and perineural invasion were also identified. Lymph node involvement could not be assessed since no lymph nodes were submitted or identified microscopically. The case was graded as pT3NxM, and the histologic type and grade were classified as moderately differentiated adenocarcinoma. The tumour was found to directly invade the liver, along with the cystic duct margin, neck margin, and liver parenchymal margin. Lymph node and distant metastasis could not be assessed.



[Table/Fig-1]: Histopathological features of clear cell carcinoma of gall bladder: a) Photomicrograph showing nests, sheets and trabeculae of cuboidal polygonal cells, with clear cytoplasm. Clear cell areas are more than 50% of tumour area. Focal areas of conventional adenocarcinoma seen {Haematoxylin and Eosin (H&E) 4X}; b) Photomicrograph showing solid nests and trabeculae of clear cells having abundant clear cytoplasm and well-defined cytoplasmic border (H&E,10X); c, d) Photomicrograph showing cells with large, well defined cytoplasmic borders, abundant clear cytoplasm, large nuclei and prominent nucleoli with mild nuclear atypia. Arranged in nests, sheets and trabeculae. Focal areas of conventional adenocarcinoma seen (H&E, 40X).
H&E: Haematoxylin and Eosin

An immunohistochemistry panel was performed, showing that the tumour cells were positive for Cytokeratin-7 (CK7) and focal positive for Carcinoembryonic Antigen (CEA), but negative for Cytokeratin-20 (CK20), Paired box transcription factor 8 (PAX8), GATA binding protein 3 (GATA3), Napsin, Wilms tumor 1 receptor (WT1), and Thyroid transcription factor 1 (TTF1) [Table/Fig-2a-i]. This eliminated the suspicion of metastatic clear cell renal carcinoma, clear cell carcinoma of the ovary, or endometrial clear cell carcinoma. The patient is currently receiving chemotherapy.



[Table/Fig-2]: Immunohistochemistry of Clear cell carcinoma of gall bladder. a) Photomicrograph showing CK7 positivity in clear cell carcinoma and in gall bladder mucosa (IHC 10X); b) Photomicrograph showing CK7 positivity in clear cell carcinoma area (IHC 40X); c) Photomicrograph showing CEA focal positivity (IHC 10X), d) Photomicrograph showing CK20 negative stain in clear cell areas (IHC 10X), e) Photomicrograph showing GATA3 negative stain in clear cell areas (IHC 10X), f) Photomicrograph showingNapsin negative stain in clear cell areas (IHC 10X), g) Photomicrograph showing PAX8 negative stain in clear cell areas (IHC 40X), h) Photomicrograph showing TTF1 negative stain in clear cell areas (IHC 10X), i) Photomicrograph showing WT1 negative stain in clear cell areas (IHC 40X).

DISCUSSION

GBC is the fifth most common malignancy of the gastrointestinal tract and the most common malignancy of the extrahepatic biliary tract [1]. The overall incidence is approximately three per 100,000 people, varying by geography and ethnicity [2]. The majority of cases are usually diagnosed incidentally after cholecystectomy by the pathologist at an advanced stage. Approximately 30% of GBC cases are diagnosed preoperatively, hence termed incidental or occult GBC. The occurrence of the clear cell variant is low (<1% of cases), while adenocarcinoma is the most common subtype, seen in almost 90% of cases.

Due to its uncommon occurrence, very little information is available regarding proper diagnosis, treatment, recurrence, prognosis, and survival rates [3,4]. GBC is a malignant tumour with an overall poor prognosis, often diagnosed at a later stage because of nonspecific signs and symptoms [1,2]. The most common sites of occurrence are the fundus (60%), body (30%), and neck (10%).

Risk factors for GBC include gallstones and specific geographic and ethnic characteristics reported in the female population of the indigenous Mapuche people of Chile. The incidence of GBC correlates with the dimensions and volume of gallstones. Chronic inflammation, inflammation caused by aflatoxin B1, Salmonella typhi, anomalous junction of the pancreaticobiliary duct, gall bladder polyps, and, rarely, familial cancer predisposition syndromes have also been implicated as risk factors [2,4].

Chronic inflammation and metabolic syndrome appear to be significant events in the development of GBC, which may take up to a decade to develop. Other risk factors include obesity, red meat consumption, and alcohol intake [5,6]. In addition to environmental risk factors, there are genetic alterations associated with GBC, such as TP53 alterations (50%), Cyclin-dependent kinase inhibitor 2A (CDKN2A) or Cyclin-dependent kinase inhibitor 2B (CDKN2B) (19%), AT-rich interaction domain-containing protein 1A (ARID1A) (13%), phosphatidylinositide 3-kinase, catalytic subunit alpha (PIK3CA) (10%), catenin beta 1 (CTNNB1) (10%), and amplification of erb-B2 receptor tyrosine kinase 2 (ERBB2) (16%) [2].

Clear cell adenocarcinoma is a rare subtype of GBC. In 1926, Tyson W and Piney A renamed and provided a proper description of clear cell carcinoma of the gall bladder and hypernephroma of the gall bladder [7]. It was first recognised by Albores-Saavedra J, Henson DE and Klimstra DS in 1986 [8].

According to the literature, the age of presentation ranges from 54 to 82 years; however, in the present study, the patient was 40 years old. The patient in the present study was female, similar to the cases reported in other studies, except for the case reported by Papatheodorou P et al., [9]. The clinical presentation and radiological findings in the present study were comparable to those described in previous reports. A brief comparison of previously reported cases in the literature with the present study, highlighting demographic, clinicoradiological, histopathological, and immunohistochemical parameters, is presented in [Table/Fig-3] [4,9-19].

The clear cell variant of GBC has histological features similar to those of metastatic renal clear cell carcinoma, hepatocellular carcinoma, metastatic adrenocortical carcinoma, clear cell thyroid carcinoma, clear cell carcinoma of the ovary, endometrial clear cell carcinoma, and clear cell carcinoma of the urinary bladder [9].

Several Immunohistochemical (IHC) markers are used to aid in the differential diagnosis. Metastatic renal cell carcinoma is PAX8 and CK20 positive but CK7 negative. Hepatocellular carcinoma shows Hepatocyte Paraffin 1 (HepPar1) and Glypican-3 positivity. Clear cell carcinoma of the ovary is HNF1-beta and Napsin positive but

No.	Authors	Age (years)/ Sex	Clinical presentation	Radiological finding	Surgical treatment	Microscopy	Immunohistochemistry and special stains	Follow-up	Country	Year of publication
1.	Maharaj R et al., [4]	56/F	Abdominal pain	USG: Calculi with fundic mass. MRCP: Tumour with calculi.	Open Cholecystectomy with lymphadenectomy	Clear cell carcinoma GB	CK7+ - positive CK20, PAX-8-Negative	Alive on chemo-therapy	USA	2017
2.	Nahid Z et al., [11]	56/F	Abdominal discomfort	USG: fundal thickening &calculi. CT: Thickened GB wall, no mass.	Laparoscopic Cholecystectomy	Clear cell carcinoma GB	Pas positive- cytoplasm	Alive	India	2022
3.	Dixit N et al., [10]	60/F	RUQ pain	USG: GB calculi.	Cholecystectomy	AFP Producing clear cell carcinoma	CK7, CK20, AFP-positive PAX8- negative	On chemo-therapy	India	2021
4.	Papatheodorou P et al., [9]	82/M	Abdominal pain	MDCT: GB perforation, ill defined foci.	Open Cholecystectomy	Clear cell carcinoma GB	CK7, CEA, CK19, EMA- Positive CK20,CK 5/6- Negative	Metastasis; Died.	Cyprus	2023
5.	Zhang C et al., [12]	80/M	Dull hypochondriac pain	CT: Solid mass	Radical resection	Clear cell carcinoma GB with hepatoid differentiation	CK19, CK 8, CK 18-positive Heppar1, glypican-positive in cells with features of hepatocytes AFP, HMB45, smooth muscle actin - Negative		Peoples Republic of China	2016
6.	Batsuuri B et al., [13]	54/F	Abdominal pain	USG: Enlarged GB with calculi. CT: GB wall thickening.	Open cholecystectomy	Clear cell carcinoma GB			Mongolia	2021
7.	Eken H et al., [14]	56/F	Abdominal pain	CT: Mass in Gb MRI: heterogenous solid mass. PET: No distant metastasis.	Laparoscopic Cholecystectomy with part of liver resection.	Clear cell carcinoma GB			Turkey	2015
8.	Sentani K et al., [15]	78/F	Epigastric pain	USG: polypoidal lesion in the Gb fundus.	Cholecystectomy with lymphadenectomy	AFP producing clear cell GB with neuroendocrine differentiation and poorly undifferentiated carcinoma.	AFP- positive in clear cells.	Disease free or 8 months	Japan	2014
9.	Vaíllo A et al., [16]	72/F	RUQ pain	CT: GB carcinoma, metastasis to liver	Trucut biopsy liver mass	Clear cell carcinoma GB	Positive- EMA, CA19-9, CK20,CK7 Negative- PAS-D, VIMENTIN, CEA, CK5/6, CK13,TTF1CHROMO GRANIN,SYNAPTOP HYSIN, ALPHAFOETO PROTEIN, HEPPAR1, THROMBOMODULIN.	Chemotherapy	Spain	2004
10.	Piana S et al., [17]	66/F	Dull hypochondriac pain	USG: Distended GB with stone	Laparoscopic Cholecystectomy	Clear cell carcinoma with small cell carcinoma	Clear cells- pas positive	Lung and skin Metastasis; died after 3 years	Italy	2002
11.	Jagtap SV et al., [18]	56/F	Abdominal pain and vomiting	USG- GB mass with calculi CT, MRCP- Thickened wall and polypoidal growth in fundus	Open cholecystectomy with lymphadenectomy	Clear cell carcinoma with hepatoid differentiation			India	2024
12.	Vardaman C and Albores Saavedra J (7 cases) [19]	56-68/F	Abdominal pain	CT- mass (in 6 cases)	Cholecystectomy	Clear cell carcinoma GB	Positive-: PAS-D, EMA, CK, Erythropoiesis-associated antige CEA and AFP positive for patient with clear cell and hepatoid differentiation. Negative: neuroendocrine markers.	5 Died 2 Alive with disease	USA	1995
13.	Present case	40/F	Abdominal pain, nausea, vomiting	USG: distended GB with calculi MRCP: thickened wall with Calculi	Cholecystectomy with CBD exploration	Clear cell carcinoma	Ck7+ , CEA= focally positive, Negative- PAX8, GATA3, CK20, TTF1, WT1, napsins,	On Chemotherapy	India	2025

[Table/Fig-3]: A brief review of literature of various studies showing demographic, clinicoradiological, histopathological and immunohistochemical parameters of clear cell carcinoma of gall bladder [4,9-19].
MDCT- Multi-detector computed tomography; CT: Computed tomography; AFP: Alpha fetoprotein; HMB45: Human melanoma black; RUQ: Right upper quadrant; PET: Positron emission tomography

Estrogen Receptor (ER) and CK7 negative. Endometrial clear cell carcinoma is ER and Hepatocyte Nuclear Factor 1-beta (HNF1β) positive with MMR expression. Metastatic adrenocortical carcinoma shows MelanA, Inhibin, and SF1 positivity. Clear cell thyroid

carcinoma is TTF-1 and Thyroglobulin positive, while clear cell carcinoma of the urinary bladder shows CK7, CK20, GATA3, PAX8, and Napsin positivity [5,9,10].

Immunohistochemistry plays an important role in differentiating clear cell carcinoma of the gall bladder from other metastatic clear cell carcinomas. We found that CK7 and CEA are positive in clear cell carcinoma of the gall bladder but negative in tumours originating from the thyroid, kidney, liver, ovary, and endometrium. Similar to our findings, Papatheodorou P et al., Dixit N et al., and Vardaman C and Albores-Saavedra J. also used these markers to establish the diagnosis [9,10,19]. In recent studies, TTF-1, PAX8, Napsin, GATA3, and CK20 have been utilised as negative markers to rule out other organ origins. Maharaj R et al., and Dixit N et al., also reported PAX8 and CK20 negativity in their studies [4,10].

The overall prognosis of GBC is poor, with a five-year survival rate of approximately 75% only when the disease is diagnosed at an early stage and treated appropriately. Complete surgical resection with negative margins is associated with a better prognosis. Perineural and perivascular invasion may or may not be useful in prognosticating the disease [2,3].

CONCLUSION(S)

We present a case of the clear cell carcinoma variant of the gall bladder, a rare entity with limited information available regarding proper diagnosis, treatment, recurrence, prognosis, and survival outcomes. It is essential to differentiate between a primary tumor and a metastatic lesion- particularly metastatic clear cell renal carcinoma- to avoid misdiagnosis and prevent delays in appropriate therapy.

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