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A case report of the clear cell variant of gallbladder carcinoma

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ABSTRACT

INTRODUCTION: Clear cell gallbladder carcinoma accounts for less than 1% of all gallbladder malignancies and demonstrates its unique histopathological characteristics in patients with no prior medical illness or familial predisposition.

PRESENTATION OF CASE: Here we present a case of a 56-year-old female, with no prior medical conditions presented with a 2-month history of upper abdominal pain. Routine hematological and biochemical tests were unremarkable. An abdominal ultrasound revealed the presence of a gallbladder calculi, and a fundic mass while magnetic resonance cholangiopancreatography revealed a 8.0 cm × 3.5 cm gallbladder mass. Computed tomography imaging excluded any distant haematogenous metastases. An open cholecystectomy with lymphadenectomy was proceeded by staging laparoscopy. Upon pathologic investigation, the morphologic and immunophenotypic features supported a diagnosis of clear cell variant of gallbladder carcinoma.

DISCUSSION: Pathological prognostications for primary clear cell gall bladder carcinomas are not well defined due to the rarity of cases and possible misidentification as secondary metastases. Foci of adenocarcinoma within the tumor along with immunohistochemical staining probes can be informative in consideration of differential diagnosis.

CONCLUSION: In these cases, clinical case management should be personalized for increased survival with the possible incorporation of next generation sequencing approaches to guide therapeutic algorithms. We discuss this exceedingly rare case of the clear cell variant of gallbladder carcinoma in detail, highlighting some of the diagnostic, and clinical challenges.

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1. Introduction

Gallbladder carcinoma is a rather uncommon malignancy with significant geographical variation with respect to incidence and prevalence. Regions and communities with the highest prevalence include Korea, Japan, Ecuador, Chile, Alaska and the American Indians [1]. Incidence ranges from 8 to 12 cases per 100 000 in males and up to 27.3 cases per 100 000 in females in those peak indigenous populations, with lower incidences (1.5 cases per 100 000) among other populations [2]. It is usually detected at an advanced stage mainly due to the ambiguity of its clinical pre-

sentation, its aggressive biology and its anatomic proximity to the liver [3]. Risk factors associated with the increased pathogenesis of gallbladder cancer include infestation, porcelain gallbladder, gallbladder polyps, primary sclerosing cholangitis, chronic infection (e.g. salmonella typhi), congenital malformations and obesity. The metaplasia-dysplasia-carcinoma sequence may frame the carcinogenesis pathway in gallbladder cancer.

The clear cell adenocarcinoma variant of gallbladder carcinoma is exceedingly rare with less known about its recurrence and overall survival. An extensive literature search identified eight case reports of clear cell gallbladder carcinoma globally in the past seventy years. To the best of our knowledge, this is the first reported case in the Community of Latin American and Caribbean States. This case report was prepared according to the Surgical Case Report (SCARE) Guidelines [4] which provides a framework for accuracy in surgical case reports.

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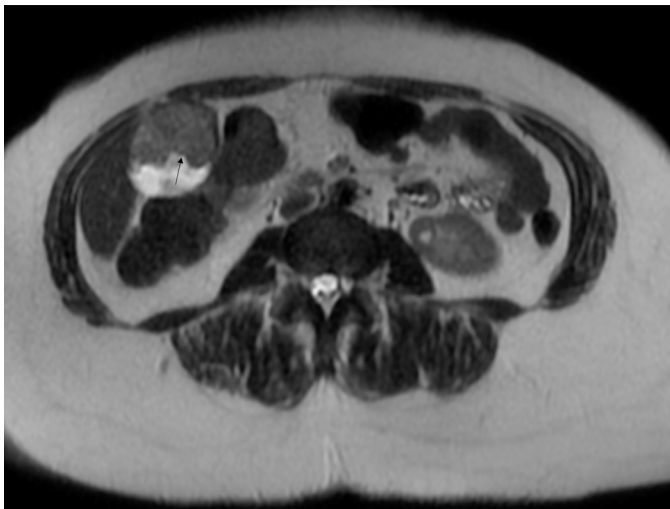


Fig. 1. T1 magnetic resonance image of gallbladder neoplasm (at arrowhead).

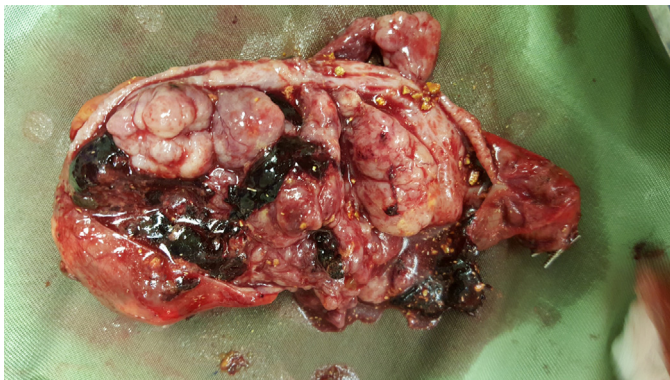


Fig. 2. Specimen image demonstrating gross morphology of the neoplasm. Surgical clips noted at the cystic duct margin.

2. Case report

A 56-year-old female with no prior medical conditions presented to the Eric Williams Medical Sciences Complex, Trinidad and Tobago with a 2-month history of upper abdominal pain. Routine hematological and biochemical tests including complete blood count, renal function tests and liver function tests were unremarkable. The patient had no history of weight loss, lymphadenopathy, fever, malaise, bone pain or respiratory issues, nor any neurological implications suggestive of metastatic or paraneoplastic manifestations.

An abdominal ultrasound revealed the presence of a gallbladder calculi, and a fundic mass which was further investigated with magnetic resonance cholangiopancreatography (MRCP) and computed tomography (CT) imaging for determination of metastatic involvement (Fig. 1). MRCP imaging revealed an 8.0 cm × 3.5 cm primary gallbladder neoplasm without any contiguous involvement of the liver bed, as well as a few gallstones, the largest of which measured 1.3 cm. CT imaging excluded any distant haematogenous metastases.

Diagnosis and management were discussed with the patient. The surgical intervention including open cholecystectomy with lymphadenectomy was preceded by staging laparoscopy. The tumor was removed without any complications (Fig. 2). Occult peritoneal disease and malignancy at the resection margin were ruled out by the adjunct of frozen sectioning of the cystic duct

margin. At the time of manuscript preparation, the patient was on Capecitabine (Xeloda, Roche) and recuperating well.

Histological assessment revealed clear cell carcinoma of the gallbladder within the fundus and body with the tumor invading the muscularis but not through the perimuscular connective tissue. All margins were surgically safe and lymph nodes from stations 8A and 12B were negative for metastatic tumor. Additionally, lymphovascular invasion was absent. Her staging based on American Joint Committee on Cancer (AJCC) guidelines was pT1_b pN0 M0; stage 1 disease. Immunohistochemical evaluation verified that the tumor arose from the mucosal surface of the gallbladder thus ruling out any renal background (Fig. 3A). The tumor cells were characterized by clear cytoplasm, well-defined cytoplasmic borders and hyperchromatic nuclei (Fig. 3B). Additionally, the tumor cells were positive for cytokeratin-7 (CK-7) and negative for cytokeratin-20 (CK-20) and paired box gene 8 (PAX8) thereby eliminating the possibility of metastatic clear cell renal carcinoma (Fig. 3C, D).

3. Discussion

Gallbladder cancer is the most common and aggressive biliary tract malignancy with the shortest median survival time [5]. Screening efforts are limited due to the paucity of symptoms as well as the lack of a cost-effective focus mechanism for early stage detection. The high rates of local recurrence and micro-metastases even for those considered surgically curable, renders clinical management challenging. Pathological prognostications of primary clear cell gall bladder carcinomas are not well established due to the rarity of cases as well as possible misidentification as secondary metastases; for example those of renal origin [6,7]. Foci of adenocarcinoma may be found within the tumor and can be informative in distinguishing primary from metastatic clear cell neoplasms along with PAX immunohistochemical staining probes [7].

Risk factors include cholelithiasis which is found in association with 80–90% of malignancies. Pure cholesterol stones greater than 1.5 cm are associated with adenosquamous and squamous cell carcinomas while increased size of the calculi may increase the risk of malignant transformation. Chronic infections by *salmonella* sp., *helicobacter pylori* and *clonorchis* sp. increase the risk for gallbladder cancer and are associated with squamous cell as well as adenosquamous malignancy. Additionally, primary sclerosing cholangitis, polyps larger than 1 cm in diameter inside the gallbladder, choledochal cysts, typhoid and opisthorchis liver disease, primary sclerosing cholangitis, porcelain gallbladder, and excessive consumption of red meat and tobacco are all reported to increase the risk [3].

With the increasing frequency of laparoscopic cholecystectomy for benign presentations there has been a concomitant increase in the incidental finding of gallbladder neoplasms [8,9]. Fortunately, this confers an increased overall survival benefit to these patients as a result of the earlier stage at detection. A retrospective analysis of gallbladder cancer cases from Johns Hopkins reported an overall five year survival of 33% associated with cases discovered incidentally, compared with 15% for those diagnosed preoperatively [8]. For incidentally detected neoplasms it is paramount to preserve the integrity of the gallbladder, obtain closure of possible breaches in the wall during dissection and use an “endobag” in retrieval of the gallbladder, in case there is need for re-operation [10]. This has been indicated for pT2 tumors but there is still controversy with respect to pT1b tumors, such as this case [11,12]. Considering her rare histological subtype, age, favorable R0 resection, satisfactory recovery, the absence of metastatic lymphadenopathy, perineural and lymphovascular invasion we decided that extensive re-operation was not necessary.

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