

CASE REPORT

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A discussion of immunohistochemistry in diagnosing a rare case of an adenosquamous carcinoma of the gallbladder

Konstantinos Damiris, Emily S Seltzer, Mark Galan, Sushil K Ahlawat

ABSTRACT

Introduction: Gallbladder cancer is rare, with adenosquamous carcinoma being an even more uncommon variant, presenting at advanced stages with right upper quadrant and epigastric pain.

Case Report: Here we describe a case of an elderly patient with extensive comorbidities presenting with weakness, pain, and unintentional weight loss who was found to have a large (11.9 × 6.2 × 6.8 cm) heterogeneous right upper quadrant mass. In an effort to provide symptomatic relief, the patient underwent an open cholecystectomy with avoidance of more extensive operations. Pathology reported invasive poorly differentiated adenosquamous carcinoma positive for cytokeratin-19 (CK-19), p63, CK 5/6, CK 8/18, and polyclonal carcinoembryonic antigen (CEA) (focal).

Conclusion: With the aid of immunohistochemistry, the tumor with extensive squamous differentiation was diagnosed as adenosquamous carcinoma of the gallbladder adenosquamous carcinoma of the gallbladder.

Keywords: Adenosquamous carcinoma, Gallbladder, Immunohistochemistry

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INTRODUCTION

Gallbladder cancer (GBC) is rare, accounting for only 1.2% of all cancer diagnoses globally, however, it is deadly as few cases are discovered in early stages [1]. A history of gallstones is associated with the highest risk of developing GBC. Unfortunately, most patients with GBC present at an advanced stage with persistent right upper quadrant and/or epigastric pain. Other presenting symptoms often include jaundice, nausea and vomiting, anorexia, weight loss, and, less commonly, a palpable mass [2]. Currently, complete surgical resection of the tumor is the only effective treatment and improves the prognosis of GBC [2]. Adenocarcinomas (AC) comprise 80–95% of all GBCs, whereas undifferentiated or aplastic carcinomas, squamous cell carcinomas (SCC), and adenosquamous carcinomas (ASC) are exceedingly rare [3]. In this study, we discuss a case of ASC of the gallbladder in which various unique immunohistochemistry markers assisted in confirming the diagnosis.

CASE REPORT

An 85-year-old male with a history of chronic pancreatitis (requiring multiple hospitalizations), alcohol abuse disorder, tobacco use disorder, hypertension, deep vein thrombosis, and pulmonary embolism presented with two days of generalized weakness and sharp right

Konstantinos Damiris¹, DO, MS, Emily S Seltzer², BS, Mark Galan³, MD, MS, Sushil K Ahlawat⁴, MD

Affiliations: ¹Department of Medicine, Rutgers New Jersey Medical School, Newark, NJ, USA; ²New York Institute of Technology College of Osteopathic Medicine, Glen Head, NY, USA; ³Department of Pathology, Immunology and Laboratory Medicine, Rutgers New Jersey Medical School, Newark, NJ, USA; ⁴Division of Gastroenterology and Hepatology, Rutgers New Jersey Medical School, Newark, NJ, USA.

Corresponding Author: Konstantinos Damiris, Department of Medicine, Rutgers New Jersey Medical School, Newark, NJ, USA; Email: kd705@njms.rutgers.edu

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upper quadrant pain. He experienced anorexia and unintentional weight loss over eight months. At baseline, he had been able to perform all activities of daily living. On exam, he appeared cachectic with a body mass index (BMI) of 16 with bitemporal wasting. He was alert and oriented to person and place only, with diffuse abdominal tenderness on palpation without rigidity or masses.

Labs on admission revealed sodium of 132 mEq/L, normocytic anemia with hemoglobin of 10.7 g/dL, alkaline phosphatase of 176 U/L, aspartate aminotransferase (AST) 28 U/L, alanine transaminase (ALT) 34 U/L, and total bilirubin of 0.9 mg/dL. About six months earlier the patient had negative carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) markers. Computed tomography (CT) showed significant enlargement of the gallbladder with a heterogeneous soft tissue density within the fundus (Figure 1), prominence of the common bile duct, and a hypodensity demonstrated within the pancreatic head potentially representing an intraductal papillary mucinous neoplasm.

The patient was medically optimized and further evaluated during his hospital course. A right upper quadrant ultrasound with Dopplers showed a heterogeneous mass with interval flow measuring 11.9 × 6.2 × 6.8 cm (Figure 2). After thorough goals of care discussion, surgeons decided to perform an open cholecystectomy with avoidance of more extensive operations such as segmental liver resection or lymphadenectomy, as per patient and family wishes.

The patient underwent an open cholecystectomy on hospital day three, during which a mass was identified on the inferior portion of the gallbladder and was opened to reveal granular, necrotic material. Microscopic examination demonstrated suspicion for gallbladder carcinoma. Intraoperative pathology consult examined the 11 × 8 × 5 cm mass and three additional tan and friable exophytic masses ranging from 2 to 2.5 cm. The largest mass appeared to invade through the gallbladder wall and into the serosal surface. Furthermore, a lymph node was appreciated during dissection, however, because the risks outweighed the benefits, it was determined that a formal portal lymphadenectomy would be foregone.

Pathology reported invasive, poorly differentiated ASC with high-grade dysplasia and areas of extensive necrosis within the gallbladder wall (Figure 3). The tumor invaded into the perimuscular connective tissue on the peritoneal side without serosal involvement (pT2a) with lymphovascular invasion, but without lymph node involvement. On immunohistochemical staining, the lesion was positive for cytokeratin-19 (CK-19), p63, CK 5/6, CK 8/18, and focal polyclonal CEA. The carcinoma had extensive squamous differentiation and was initially believed to be a poorly differentiated SCC, but pathology regarded it as adenosquamous due to the presence of columnar precursor and focal CEA expression (Figure 4). During the post-operative time frame, the patient's pain was well controlled, and the wound healed appropriately.



Figure 1: Axial CT scan image showing distended gallbladder with a heterogeneous mass within (arrow).

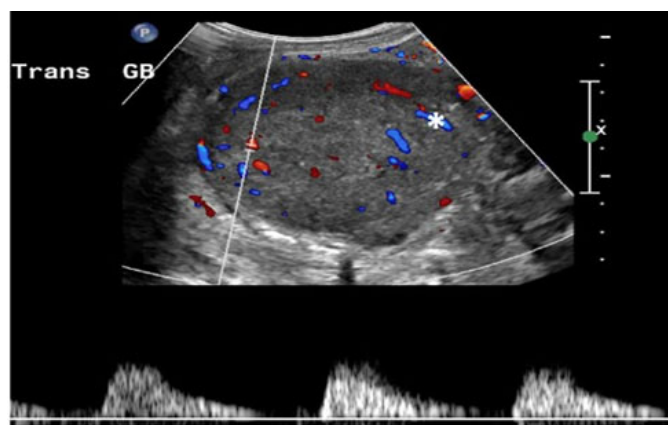


Figure 2: Right upper quadrant (RUQ) ultrasound showing gallbladder mass with internal blood flow (asterisk).

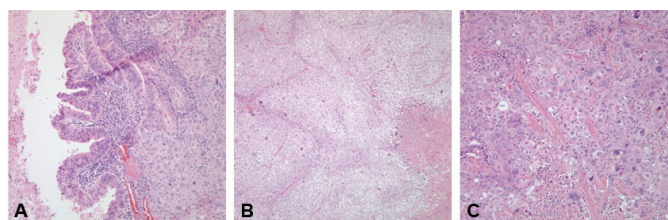


Figure 3: Hematoxylin and eosin stain. (A) High-grade dysplasia of the gallbladder epithelium with underlying invasive carcinoma showing squamous features (200×). (B) Focal necrotic carcinoma with squamous features (100×). (C) High-grade carcinoma with squamous features (200×).

DISCUSSION

Adenosquamous carcinoma of the gallbladder contains both squamous and glandular differentiation. There are no clear criteria regarding the quantity of squamous differentiation, but it can commonly be defined as having a 25–99% squamous composition [4, 5]. In our case, the tumor displayed extensive squamous differentiations and

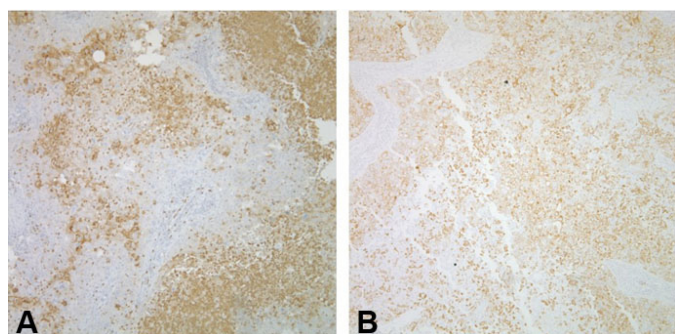


Figure 4: Immunohistochemical stain. (A) Carcinoembryonic (CEA) stain showing focal positivity in the tumor cells suggestive of adenosquamous carcinoma when coupled with high-grade dysplasia (100x). (B) Cytokeratin 5/6 (CK 5/6) highlighting squamous differentiation of the tumor (100x).

was regarded as adenosquamous due to the presence of columnar precursors and focal CEA expression.

In this case, immunohistochemistry, with adequate control, was positive for CK-19, p63, CK5/6, CK8/18, and polyclonal CEA. A positive CK5/6 stain provides strong evidence for squamous differentiation, whereas a positive CK8/18 provides strong evidence for adenocarcinoma [6]. Extrahepatic pancreatobiliary adenocarcinomas often express cytokeratins CK7, CK17 and CK19, mucin MUC1 and MUC5AC, and tumor-associated epithelial markers including CA19-9, monoclonal CEA, CA125, and maspin [7]. The expression of p63 has been shown as a poor prognostic factor in gallbladder adenocarcinoma [8]. While the consensus differs in the number of squamous cells required to diagnose ASC, there is potential in utilizing immunohistochemistry, in addition to histological findings, to confirm such diagnosis in GBC. The literature is limited on the prognostic factors of such immunohistochemistry markers in the case of ASC specifically, likely due to the rarity of the cancer.

Patients with AC and ASC of the gallbladder do not differ in age, gender, race, presence of gallstones, clinical symptoms, or serum tumor marker levels [9, 10]. Murimwa et al. compared ASC (n = 703) with AC (n = 12,455) and found ASCs to be significantly larger, with poorly differentiated components, positive surgical margins, and at more advanced stages [9]. Patients demonstrated worse survival in both the resected and unresected cohorts. They saw post-resection median survival of 10.3 months in ASC and 20.5 months in AC, whereas other studies have seen it to be as low as 3.3 and 6.0 months, respectively [9, 10]. This difference may be due to adjuvant therapy use, however, its use is still controversial in GBCs. These lengths of time are based on those achieving R0 resection, and unfortunately, in our patient, a full resection was not possible due to increased risk of complications.

CONCLUSION

In conclusion, we presented a case of an elderly male with pain and weight loss, found to have a large mass within the gallbladder. Resection was performed as a palliative effort to relieve pain and intraoperatively was found to have an invasive, poorly differentiated GBC. While the patient was believed to have SCC initially, we displayed how immunohistochemistry may further aid in revealing a diagnosis of ASC.

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Author Contributions

Konstantinos Damiris – Conception of the work, Design of the work, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related

to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Emily S Seltzer – Design of the work, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Mark Galan – Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Sushil K Ahlawat – Conception of the work, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Guarantor of Submission

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Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.

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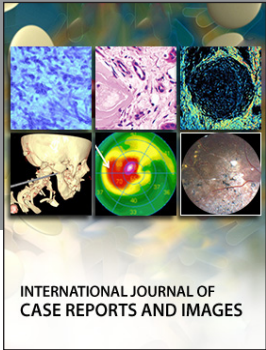
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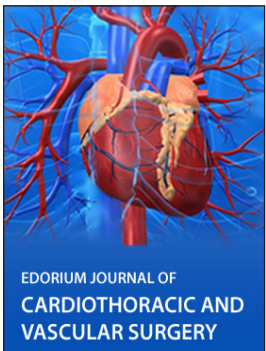
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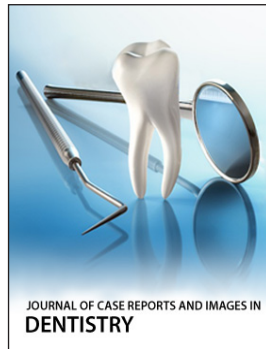
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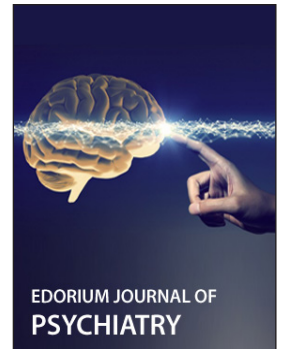
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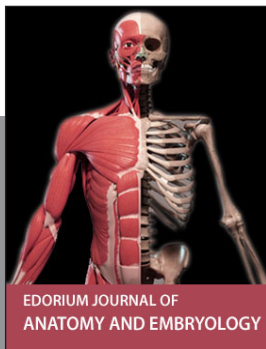
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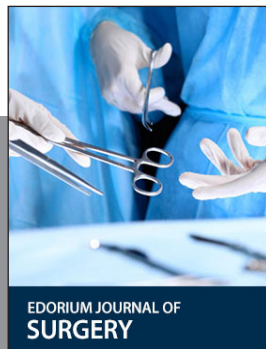
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