Case Report

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Mixed Neuroendocrine and Non-Neuroendocrine Neoplasm of the Gallbladder: Adenosquamous Carcinoma with Small Cell Neuroendocrine Differentiation – A Case Report

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ABSTRACT

Background & Objectives: Gallbladder carcinoma is an aggressive malignancy, with adenocarcinoma being the most common histological subtype. Adenosquamous carcinoma is a recognized but uncommon variant, while the presence of small cell neuroendocrine differentiation within adenosquamous carcinoma of the gallbladder is exceedingly rare and associated with poor prognosis.

Case Presentation: We report the case of a 66-year-old female who presented with right hypochondrial pain and jaundice. Histopathological examination of a simple cholecystectomy specimen revealed an infiltrating neoplasm exhibiting glandular architecture, squamoid differentiation, and sheets of small round cells predominantly on the serosal aspect. Immunohistochemistry showed p63 and CK positivity in squamoid nests and neoplastic glands respectively, and synaptophysin positivity in the small cell component, confirming neuroendocrine differentiation. The tumor perforated the serosa (pT3), with perineural invasion present and serosal margin involvement.

Conclusion: Adenosquamous carcinoma of the gallbladder with small cell neuroendocrine differentiation is a rare and aggressive entity. Accurate histopathological evaluation with immunohistochemistry is essential for correct diagnosis and prognostication.

KEY WORDS: Gallbladder carcinoma, Adenosquamous carcinoma, Neuroendocrine differentiation, Small cell carcinoma, Histopathology, Case report

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INTRODUCTION

Gallbladder carcinoma is the most common malignancy of the biliary tract and is characterized by an aggressive clinical course and poor prognosis.[1] The majority of gallbladder malignancies are adenocarcinomas; however, several histological variants have been described, including adenosquamous carcinoma and neuroendocrine carcinoma.[1,2] Adenosquamous carcinoma is a recognized but uncommon subtype that exhibits both glandular and squamous differentiation and is frequently associated with more aggressive behavior than conventional adenocarcinoma.[2,3]

Neuroendocrine differentiation in gallbladder carcinoma is rare.[4] Mixed neuroendocrine and non-neuroendocrine neoplasms (MiNENs) of the gallbladder represent an unusual and poorly characterized pathological entity.[5] The coexistence of adenosquamous carcinoma with small cell neuroendocrine differentiation is exceedingly uncommon and poses significant diagnostic as well as prognostic challenges.[6]

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Herein, we report a rare case of mixed neuroendocrine and non-neuroendocrine carcinoma of the gallbladder composed of adenosquamous carcinoma with small cell neuroendocrine differentiation, highlighting its histopathological features and clinical significance.

CASE PRESENTATION

A 66-year-old female presented with right hypochondrial pain and jaundice. MRCP without contrast was done which showed common bile duct measuring 9.6mm with multiple intraluminal filling defects, likely calculi. Final impression of MRCP without contrast was Cholelithiasis and Choledocholithiasis. Later ERCP was performed which revealed that selective CBD cannulation was done via guidewire. Contrast dye injected. Cholangiogram showed moderately dilated CBD with upstream biliary dilatation. Ample sphincterotomy done and multiple stones were extracted. Based on clinical suspicion of gallbladder pathology and cholelithiasis, the patient underwent laparoscopic cholecystectomy which was later converted to open cholecystectomy.

The specimen was received in formalin labeled as gallbladder with a surgical number and request form. It consisted of a distorted and already cut open gallbladder measuring 5.5 × 3.5 × 2 cm in aggregate. The cystic duct margin, neck and part of body were identified. However, no intact fundus was present. There were also fragmented

pieces of grey-white tissue measuring 4.3 × 3.1 × 1.2 cm in aggregate. Few green-black stones were present separately in the syringe. The mucosa was flattened and the maximum wall thickness measured 0.3 cm. Liver bed was not identified. Representative sections from fundus, body, neck, and cystic duct were submitted in blocks A–B. On regrossing, additional sections from the growth were submitted in blocks R1–R3, and the entire specimen was subsequently processed in blocks R4–R7.

Histological examination revealed an infiltrating malignant neoplasm arranged predominantly in glandular architecture as shown in Figure 1. The glands were lined by neoplastic cells showing pleomorphic, hyperchromatic nuclei and moderate cytological atypia. Intermixed groups and nests of squamoid cells were seen infiltrating the muscularis propria, consistent with squamous differentiation, Figure 2.

Additionally, focal areas demonstrated sheets and clusters of small round cells with scant cytoplasm, finely granular chromatin, and prominent crush artifact. These small cell components were predominantly located along the serosal aspect of the tumor as shown in figure 3. The tumor perforated the serosa (visceral peritoneum). Perineural invasion was present while lymphovascular invasion was not identified.

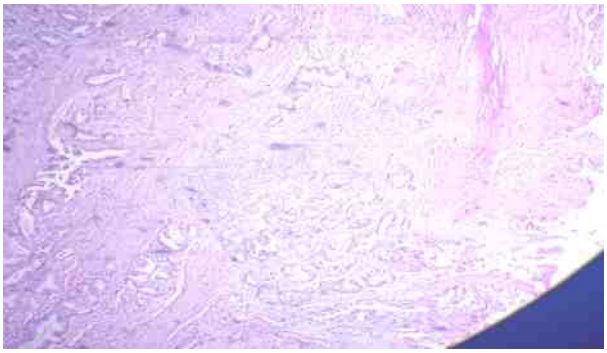

Figure 1: Tumor arranged in glands

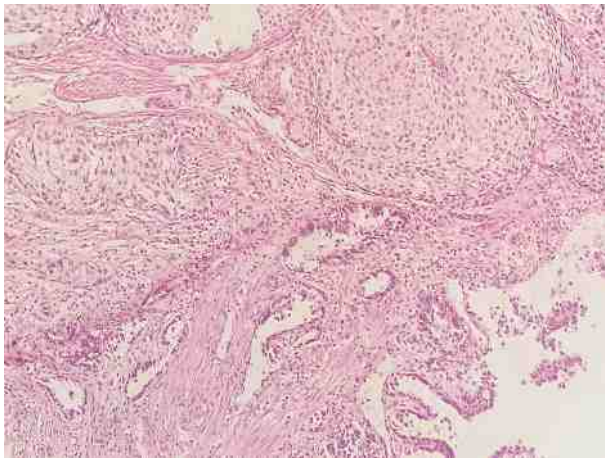

Figure 2: Both squamoid and glanduler components are present next to each other.

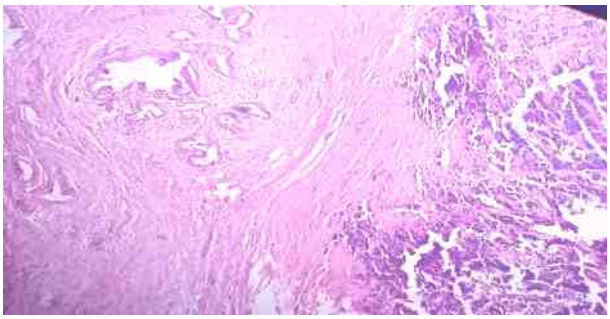

Figure 3: Tumor with both components. Left side shows glandular architecture. Right side shows small cell neuroendocrine differentiation.

Immunohistochemistry:

CK showed positivity in the squamoid nests and neoplastic glandular component, Figure 4. Synaptophysin was positive in the small cell population, confirming neuroendocrine differentiation and was negative in squamoid and glandular areas adjacent to it as shown in Figure 5. Ki-67 was 70% - 80% in small cell neuroendocrine differentiation area as shown in figure 6 and 80-90% in squamoid nests.

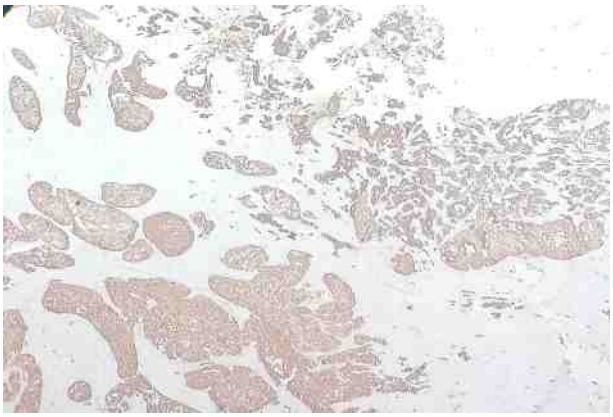

Figure 4: CK; Positive in squamoid and glandular areas.

Figure 5: Synaptophysin positivity in neuroendocrine portion of tumor.

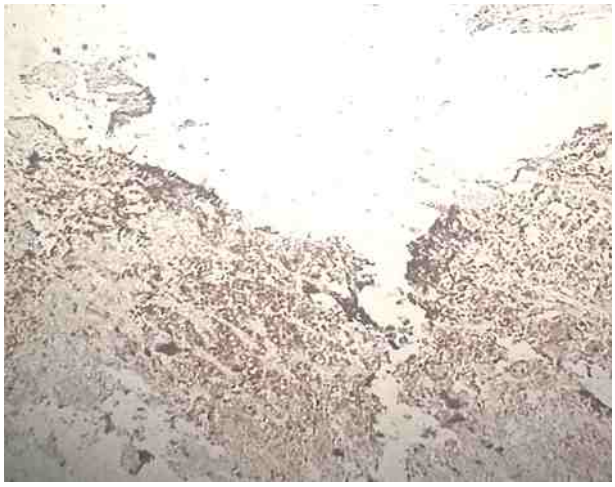

Figure 6: 70-80% Ki-67 in small cell neuroendocrine portion.

Final pathological staging and Diagnosis:

Specimen: Gallbladder (Simple cholecystectomy) Diagnosis: Mixed neuroendocrine and non-neuroendocrine carcinoma – Adenosquamous carcinoma with small cell neuroendocrine differentiation (G2, moderately differentiated).

Cholilithiasis.

Tumor Site: Fundus, body, and neck

Tumor Size: 4.3 × 3.1 × 1.2 cm (aggregate fragmented pieces)

Tumor Extent: Perforates serosa (visceral peritoneum) – pT3

Perineural Invasion: Present

Lymphovascular Invasion: Not identified

Margins:

- Cystic duct margin: Free of tumor

- Serosal margin: Involved by tumor

Regional Lymph Nodes: Not applicable (not submitted or found)

DISCUSSION

Adenosquamous carcinoma of the gallbladder is a recognized histological variant of adenocarcinoma characterized by the presence of both glandular and squamous components and is associated with aggressive biological behavior and poorer prognosis compared with conventional adenocarcinoma.[2,3] The presence of a neuroendocrine component, particularly of the small cell type, further worsens the prognosis because of its high proliferative activity, early invasion, and increased metastatic potential.[4,6]

Mixed neuroendocrine and non-neuroendocrine neoplasms (MiNENs) of the gallbladder are exceedingly rare and present significant diagnostic challenges due to their heterogeneous morphology and overlapping histological features.[5] According to the current World Health Organization (WHO) classification, MiNENs are defined as neoplasms composed of both neuroendocrine and non-neuroendocrine components, each constituting at least 30% of the tumor.[4,5]

Only a limited number of cases of gallbladder carcinomas with combined adenosquamous and neuroendocrine differentiation have been described in the literature. Jung et al. reported a case of combined adenosquamous carcinoma with large cell neuroendocrine carcinoma of the gallbladder, highlighting the aggressive clinical course and poor prognosis associated with such mixed tumors.[6] Similarly, other studies have emphasized that neuroendocrine differentiation within gallbladder carcinoma is associated with rapid tumor progression, early lymphovascular invasion, and a higher likelihood of distant metastasis.[3,6]

In the present case, the coexistence of glandular, squamoid, and small cell neuroendocrine components was confirmed both morphologically and immunohistochemically. Immunohistochemical staining demonstrated p63 positivity in the squamoid component and synaptophysin positivity in the small cell neuroendocrine component, supporting the diagnosis of a mixed neoplasm.[4,7]

The main differential diagnoses include poorly differentiated adenocarcinoma, pure small cell neuroendocrine carcinoma, and carcinoma with focal squamous metaplasia. Careful histomorphological assessment supplemented by an appropriate immunohistochemical panel is essential for accurate classification and to avoid under-recognition of the neuroendocrine component.[4,5]

Furthermore, the presence of serosal perforation (pT3), perineural invasion, and serosal margin involvement in this case indicates an advanced and biologically aggressive tumor. Previous studies have reported that adenosquamous carcinoma with neuroendocrine differentiation of the gallbladder is an exceptionally rare entity and is associated with a significantly worse prognosis compared with conventional gallbladder adenocarcinoma.[3,6]

Recognition of this rare histological combination is important for accurate diagnosis, appropriate classification, and prognostic assessment, as the neuroendocrine component may influence therapeutic strategies and clinical outcomes.

CONCLUSION

Adenosquamous carcinoma of the gallbladder with small cell neuroendocrine differentiation is an extremely rare and aggressive malignancy. This case emphasizes the importance of thorough histopathological examination and immunohistochemical evaluation for identifying mixed tumor components. Early recognition of this entity is crucial for prognostication and guiding clinical management due to its poor prognostic implications.

Patient consent:

Written informed consent was obtained from the patient for publication of this case report and associated histopathological details.

Conflict of interest: None

Financial Disclosure: None

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