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Pathology

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MIXED NEUROENDOCRINE–NON-NEUROENDOCRINE NEOPLASM OF THE GALLBLADDER: A RARE CASE REPORT

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ABSTRACT

Mixed neuroendocrine–non-neuroendocrine neoplasms (MiNENs) of the gallbladder are extraordinarily uncommon and represent a unique diagnostic challenge due to their bimodal cellular composition and aggressive biological behavior. These tumors contain both a neuroendocrine carcinoma (NEC) component and a non-neuroendocrine epithelial malignancy, each comprising at least 30% of the tumor .We report a gallbladder MiNEN in a 74-year-old male who presented with abdominal pain, vomiting, and fever. Imaging revealed a gallbladder mass, and cholecystectomy with lymph node dissection was performed. Histopathological examination demonstrated a dual tumor composed of well-differentiated adenocarcinoma and high-grade neuroendocrine carcinoma. Immunohistochemistry showed strong positivity for synaptophysin and focal chromogranin expression within the NEC component, with a proliferative index (Ki-67) of 75%. The final staging was pT3 pN1. This case highlights the role of meticulous histopathological assessment and immunohistochemistry in diagnosing MiNENs, especially in organs where neuroendocrine cells are typically absent.

INTRODUCTION

Gallbladder carcinoma is the fifth most frequent malignancy arising within the digestive tract. Although adenocarcinoma constitutes the predominant histological subtype, several rare variants exist, including neuroendocrine carcinoma and mixed tumors containing neuroendocrine and non-neuroendocrine components. Primary neuroendocrine tumors of the gallbladder account for fewer than 1% of all neuroendocrine neoplasms and approximately 2% of gallbladder cancers. MiNENs are classified by the World Health Organization (WHO) as tumors containing two malignant components: a neuroendocrine element and a non-neuroendocrine carcinoma, each constituting at least 30% of the tumor mass. Although MiNENs are documented throughout the gastrointestinal tract, their occurrence in the gallbladder is particularly uncommon. The limited number of reported cases restricts our understanding of their biological behavior, optimal treatment approaches, and prognostic indicators. Because gallbladder mucosa does not normally contain neuroendocrine cells, the development of neuroendocrine tumors in this location is believed to be associated with chronic inflammation—most commonly secondary to gallstones—resulting in intestinal or pyloric metaplasia and the appearance of neuroendocrine differentiation. This case adds to the limited pool of documented gallbladder MiNENs and underscores the importance of accurate pathological evaluation in identifying such tumors.

Aims and Objectives

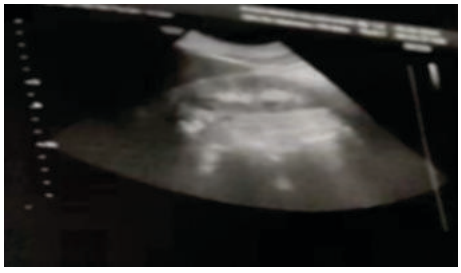
1) To present a rare case of mixed neuroendocrine–non-neuroendocrine neoplasm of the gallbladder.
2) To describe the clinical, radiological, gross, microscopic, and immunohistochemical features in detail.
3) To discuss the diagnostic challenges associated with MiNENs.
4) To contextualize the case with current literature and the WHO 2019 classification criteria.

MATERIALS AND METHODS

This case report is based on clinical records, imaging findings, and histopathological evaluation of a gallbladder specimen submitted to the Department of Pathology. Standard hematoxylin and eosin (H&E) staining was performed. Immunohistochemical testing involved synaptophysin, chromogranin A, and Ki-67 to clarify the nature of the neuroendocrine component. Relevant journal articles, WHO tumor classification guidelines, and case studies were reviewed to support the discussion.

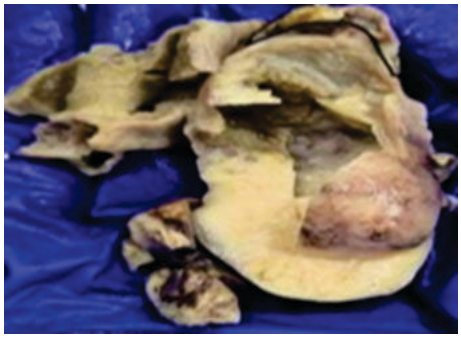
Clinical Presentation

A 74-year-old male presented with complaints of abdominal pain, recurrent vomiting, and fever persisting for 18 days. There was no remarkable history of weight loss, jaundice, or gastrointestinal bleeding. Physical examination showed right upper quadrant tenderness. Laboratory tests revealed mild leukocytosis, while liver function tests were normal. Ultrasonography of the abdomen demonstrated asymmetrical thickening of the gallbladder wall along with a soft-tissue mass measuring 37 × 32 mm. With a presumptive diagnosis of gallbladder malignancy, the patient underwent cholecystectomy with removal of regional lymph nodes.



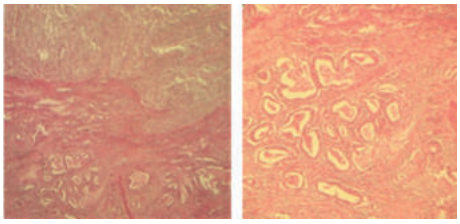
Gross Pathology

The cholecystectomy specimen measured 8 cm in length. The serosal surface appeared congested, and the gallbladder wall was markedly thickened. Sectioning revealed an ulceroinfiltrative tumor occupying the body and fundus. The lesion was firm, grey-white, and infiltrative, with focal areas of necrosis. A solitary lymph node submitted separately measured 1.2 cm.



Microscopic Examination

Histological examination revealed a biphasic malignant neoplasm composed of:



1. Non-neuroendocrine Component

This portion showed a well-differentiated adenocarcinoma arranged in tubular and gland-forming patterns. The lining epithelial cells exhibited stratification, mild-to-moderate nuclear atypia, and occasional mitotic figures. Tumor infiltration extended through the muscular layer into the perimuscular connective tissue, corresponding to pT3.

2. Neuroendocrine Carcinoma Component

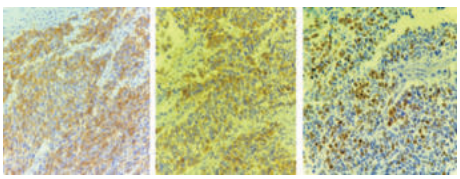
The second component consisted of a high-grade neuroendocrine carcinoma characterized by: small-to-intermediate-sized cells, hyperchromatic nuclei, scant cytoplasm, nuclear molding, abundant mitotic figures, extensive necrosis. These features were consistent with a poorly differentiated neuroendocrine carcinoma. The two components were interspersed yet distinct, and each exceeded 30% of the tumor, fulfilling WHO criteria for MiNEN.

One of the regional lymph nodes demonstrated metastatic deposits derived from the neuroendocrine carcinoma component, confirming pN1 status.

Immunohistochemistry

IHC played a crucial role in classifying the tumor. The neuroendocrine carcinoma component showed:
Strong, diffuse synaptophysin positivity and Focal chromogranin A positivity with Ki-67 proliferation index of 75%, indicating a highly aggressive phenotype.

The adenocarcinoma portion lacked neuroendocrine marker expression. These findings supported the final diagnosis of MiNEN composed of adenocarcinoma and high-grade neuroendocrine carcinoma.



RESULTS

A diagnosis of Mixed Neuroendocrine–Non-Neuroendocrine Neoplasm (MiNEN) of the gallbladder, pT3pN1 was established. The high Ki-67 index indicated rapid tumor proliferation. The pathology report was communicated to the surgical and oncology teams for further management planning.

DISCUSSION

MiNENs are rare composite tumors that contain both a neuroendocrine carcinoma and a conventional epithelial malignancy. Although these tumors have been described in several gastrointestinal organs, their occurrence in the gallbladder is extremely uncommon. The rarity of these lesions contributes to the incomplete understanding of their pathogenesis and optimal management strategies.

PATHOGENESIS

Since neuroendocrine cells are typically absent in the normal gallbladder epithelium, their emergence is hypothesized to occur through metaplastic transformation triggered by chronic inflammation, especially cholelithiasis. Intestinal metaplasia in chronically inflamed gallbladders may provide a niche for neuroendocrine differentiation.

Clinical Challenges

Patients with gallbladder MiNENs often present with non-specific symptoms such as abdominal pain, nausea, or fever, which can mimic benign inflammatory conditions. This similarity frequently leads to delayed diagnosis. Imaging techniques are insufficient to distinguish MiNEN from typical adenocarcinoma and thus histological and immuno-histochemical analysis remains essential.

Diagnostic Consideration

WHO 2019 criteria require that both the neuroendocrine and non-neuroendocrine components constitute at least 30% of the tumor. The neuroendocrine component is usually the more aggressive part and tends to dictate prognosis. In our case, the NEC component exhibited a Ki-67 index of 75%, suggesting rapid proliferation and increased metastatic potential.

Prognosis

Prognosis depends heavily on the grade of the neuro-endocrine component. High-grade NECs are associated with early metastasis, poor response to therapy and reduced survival. Lymph node involvement, as seen in this case, further worsens outcomes.

Management

Surgical resection remains the primary treatment for localized disease. Given the aggressive nature of NEC, platinum-based chemotherapy regimens similar to those used for small-cell carcinomas are commonly recommended. Research into targeted therapy and immunotherapy is ongoing, but standardized treatment guidelines are yet to be established.

Comparison with Literature

Published case reports—including those by Chen et al. and others—emphasize the rarity and poor prognosis of gallbladder neuroendocrine tumors. WHO classification updates have strengthened the distinction of MiNENs as independent pathological entities, underscoring the necessity of detailed pathological evaluation.

CONCLUSION

Gallbladder MiNENs represent a highly uncommon yet aggressive form of malignancy. Due to their subtle clinical presentation and rarity, diagnosis often depends on careful histopathological examination supported by immuno-histochemistry. Recognizing the presence of both tumor components is vital, as treatment and prognosis differ from conventional adenocarcinomas. Reporting new cases helps broaden current understanding and contributes to the evolving literature on this rare neoplasm.

Declaration

The authors declare no conflict of interest.

REFERENCES

1) Chen H, Shen YY, Ni XZ. Two cases of neuroendocrine carcinoma of the gallbladder. World J Gastroenterol. 2014;20(33):11916–11920.
2) Klimstra D, Klöppel G, La Rosa S, Rindi G. Classification of neuroendocrine neoplasms of the digestive system. In: WHO Classification of Tumours Editorial Board, ed. Digestive System Tumours. 5th ed. Lyon: IARC; 2019: 16–19.
3) Costa AC, Cavalcanti CLC, Coelho HGB, Leão LHA, Soares DTC, Santa-Cruz F, Paz AR, Ferraz ÁAB. Rare Mixed Adenoneuroendocrine Carcinoma of the Gallbladder: Case Report and Review of Literature. Am J Case Rep. 2021 May 4;22:e929511. DOI: 10.12659/AJCR.929511. PMID: 33945521;PMCID: PMC8105744.
4) Ren X, Jiang H, Sun K, Qin X, Qu Y, Xia T, et al. Mixed neuroendocrine-non-neuroendocrine neoplasm of the gallbladder: case report and literature review. Diagn Pathol. (2022) 17:51. doi: 10.1186/s13000-022-01231-6.