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Neuroendocrine Tumor of Gallbladder—A Rare High-Grade Malignancy

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Abstract

Gallbladder neuroendocrine tumors are uncommon neoplasms and constitute only a minor proportion of neuroendocrine as well as gallbladder malignancies. Patients commonly present with vague symptoms, resulting in diagnosis at an advanced stage of disease. We describe one such rare case of a 41-year-old male diagnosed with a high-grade (Grade 3) neuroendocrine tumor of the gallbladder with hepatic invasion. Histopathological examination and immunohistochemistry confirmed the diagnosis. This case highlights the aggressive nature of gallbladder NETs and the importance of histopathological evaluation and proliferative indices in diagnosis, grading, and prognosis.

Keywords: Cholecystectomy, Gallbladder, Diagnosis, Necrosis, PET scan

Introduction

Neuroendocrine tumors are a diverse group of epithelial neoplasms that arise from cells capable of neuroendocrine differentiation. These tumors are most frequently found in the gastrointestinal tract and bronchopulmonary system, while their presence in the gallbladder is extremely uncommon, with an estimated incidence of approximately 0.2%.[1,2] The low incidence is attributed to the relative absence of native neuroendocrine cells in normal gallbladder mucosa.[3] It is unclear how gallbladder NETs develop. However, it is believed that long-term inflammatory diseases like cholelithiasis and cholecystitis cause metaplastic alterations, which may encourage the growth of neuroendocrine cells and their eventual malignant transformation. [4, 5] Clinically, these tumors often present with vague abdominal symptoms and are frequently discovered incidentally following surgical resection.[6]

Case Report

A 41-year-old male presented with a one-month history of persistent abdominal pain associated with bloating. There was no significant past medical or surgical history. Ultrasonography (USG) revealed an ill-defined lesion in the gallbladder fossa, with the gallbladder not separately visualized. PET scan (positron emission tomography) showed increased metabolic activity in a large soft tissue mass involving the gallbladder and adjacent hepatic parenchyma, raising suspicion of malignancy. The clinical diagnosis was carcinoma of the gallbladder.

Radical cholecystectomy with resection of the adjacent liver margin was performed. The specimen included a portion of liver and an attached tumor altogether

measuring 7.5 × 4 × 2 cm. The cut surface showed a grey-white, poorly defined tumor with necrosis; the main tumor size was about 5.2 × 4 cm, indicating aggressive malignancy (Fig. 1).

Scrape cytology revealed salt-and-pepper chromatin (Fig. 2).

H&E-stained sections revealed a tumor composed of relatively uniform cells arranged in sheets and organoid nests. The tumor cells displayed round to oval nuclei with finely granular "salt-and-pepper" chromatin and moderate eosinophilic cytoplasm. Focal areas of necrosis were present (Fig. 3). Adenocarcinoma of the gallbladder & neuroendocrine tumor of the gallbladder were the differential diagnosis.

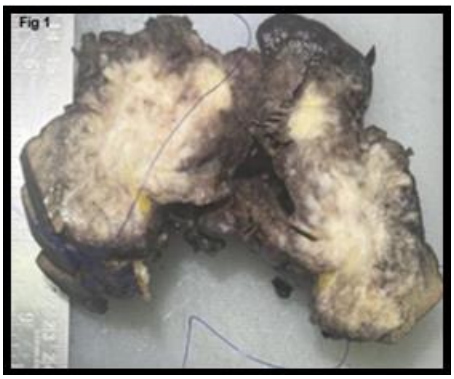

Fig 1: Gross photograph showing a poorly circumscribed tumor with a grey, white cut surface.

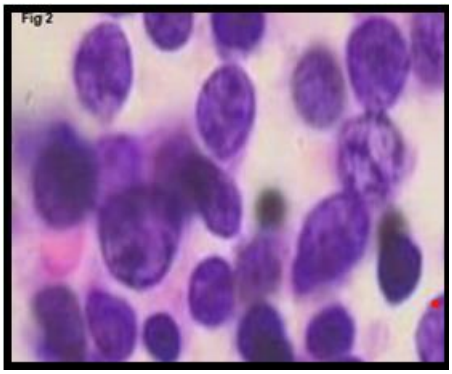

Fig 2: Scrape cytology showing salt and pepper chromatin.

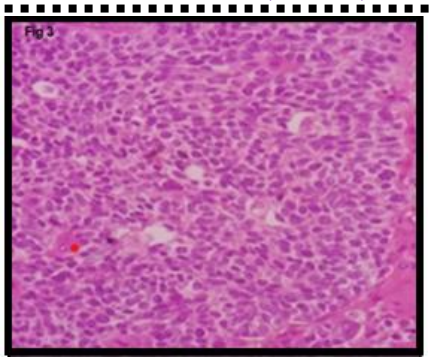

Fig 3: H&E Sections showing uniform cells arranged in sheets and organoid nests round to oval nuclei with finely granular "salt-and-pepper" chromatin and moderate eosinophilic cytoplasm.

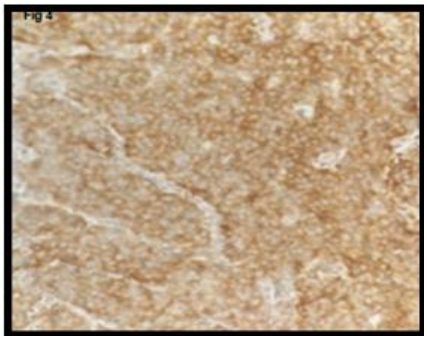

Fig 4: Synaptophysin: Diffuse strong cytoplasmic positivity.

Fig 5: Chromogranin positivity

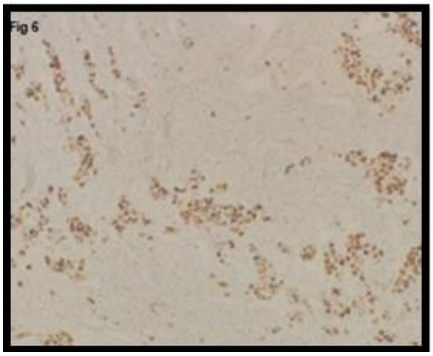

Fig 6: Ki 67 >50%

Immunohistochemical studies demonstrated strong positivity for synaptophysin (Fig. 4) and chromogranin (Fig. 5), confirming neuroendocrine origin. The Ki-67 proliferation index (Fig. 6) was greater than 50%, consistent with a high-grade (Grade 3) neuroendocrine carcinoma as per established classification systems[9, 10.]

Discussion

Primary neuroendocrine tumors of the gallbladder are rare but clinically significant due to their aggressive nature and poor prognosis. Epidemiological studies indicate that NETs of the gallbladder account for less than 2% of all gallbladder tumors and approximately 0.2% of all neuroendocrine neoplasms [2].

The diagnosis of these tumors prior to surgery remains difficult. Imaging modalities such as ultrasonography, CT, MRI, and PET-CT are useful in detecting gallbladder masses but lack specificity in differentiating NETs from adenocarcinomas or other malignancies[6.]

A definitive diagnosis is established primarily through histopathological evaluation. The presence of organoid architecture, uniform tumor cells, and characteristic nuclear chromatin pattern provides important diagnostic clues[7.] However, confirmation requires immunohistochemical staining, with synaptophysin and chromogranin being the most reliable markers.

Assessment of the Ki-67 proliferative index plays a major role in tumour grading and prediction of biological behaviour. According to WHO classification, tumors with a Ki-67 index greater than 20% are classified as Grade 3 and are associated with aggressive clinical behaviour and poor outcomes[9].

Tumor size and extent of invasion are also critical prognostic factors. Lesions larger than 2 cm are more likely to demonstrate hepatic invasion and lymph node metastasis at presentation[5.] The presence of liver infiltration in this case further supports the advanced stage of disease.

Recent studies and population-based analyses have shown that gallbladder NETs frequently present at an advanced stage, contributing to poor survival outcomes. Despite advances in diagnostic techniques, early detection remains a challenge.

Management and Prognosis

Surgery remains the preferred treatment option in patients with localized disease. In cases with liver involvement, extended surgical procedures may be necessary to achieve complete tumor removal[6]. High-grade neuroendocrine carcinomas often require multimodal treatment approaches, including chemotherapy and targeted therapies. However, the prognosis remains poor due to rapid disease progression and early metastasis.

Conclusion

Neuroendocrine tumors of the gallbladder are rare and aggressive malignancies that pose significant diagnostic challenges. Their nonspecific clinical presentation often leads to delayed diagnosis. Histopathological examination, supported by immunohistochemistry and proliferation indices, is essential for accurate diagnosis and grading. Early detection and aggressive management are crucial; however, high-grade tumors are associated with poor prognosis.

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