



Case Report

# Neuroendocrine carcinoma of gallbladder: A rare entity

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## ABSTRACT

Gallbladder neuroendocrine carcinoma is a rare neoplasm thought to arise in the background of chronic inflammation triggered by cholelithiasis. The symptoms of this tumor overlap with those of cholecystitis and other carcinomas of the gall bladder. The imaging findings with fine needle aspiration cytology help in the pre-operative diagnosis. However, the gold standard for diagnosis is histopathology evaluation with immunohistochemistry.

We report a case of a 76-year female who was clinically diagnosed with acute calculus cholelithiasis and underwent surgery. The histopathology and immunohistochemistry of the gallbladder revealed neuroendocrine carcinoma.

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## INTRODUCTION

Neuroendocrine neoplasms (NEN) are rare neoplasms that were first reported by Oberndorfer in 1907.<sup>1</sup> These neoplasms arise from neuroendocrine cells and hence commonly occur in sites like the respiratory tract and the gastrointestinal tract, where neuroendocrine cells are abundantly distributed. The gallbladder is a rare site for this tumor as the gallbladder, except for the neck, lacks neuroendocrine cells.<sup>2</sup> The Surveillance, Epidemiology, and End Results (SEER) programs registry reports NEN of the gallbladder comprising of 0.5% of all neuroendocrine

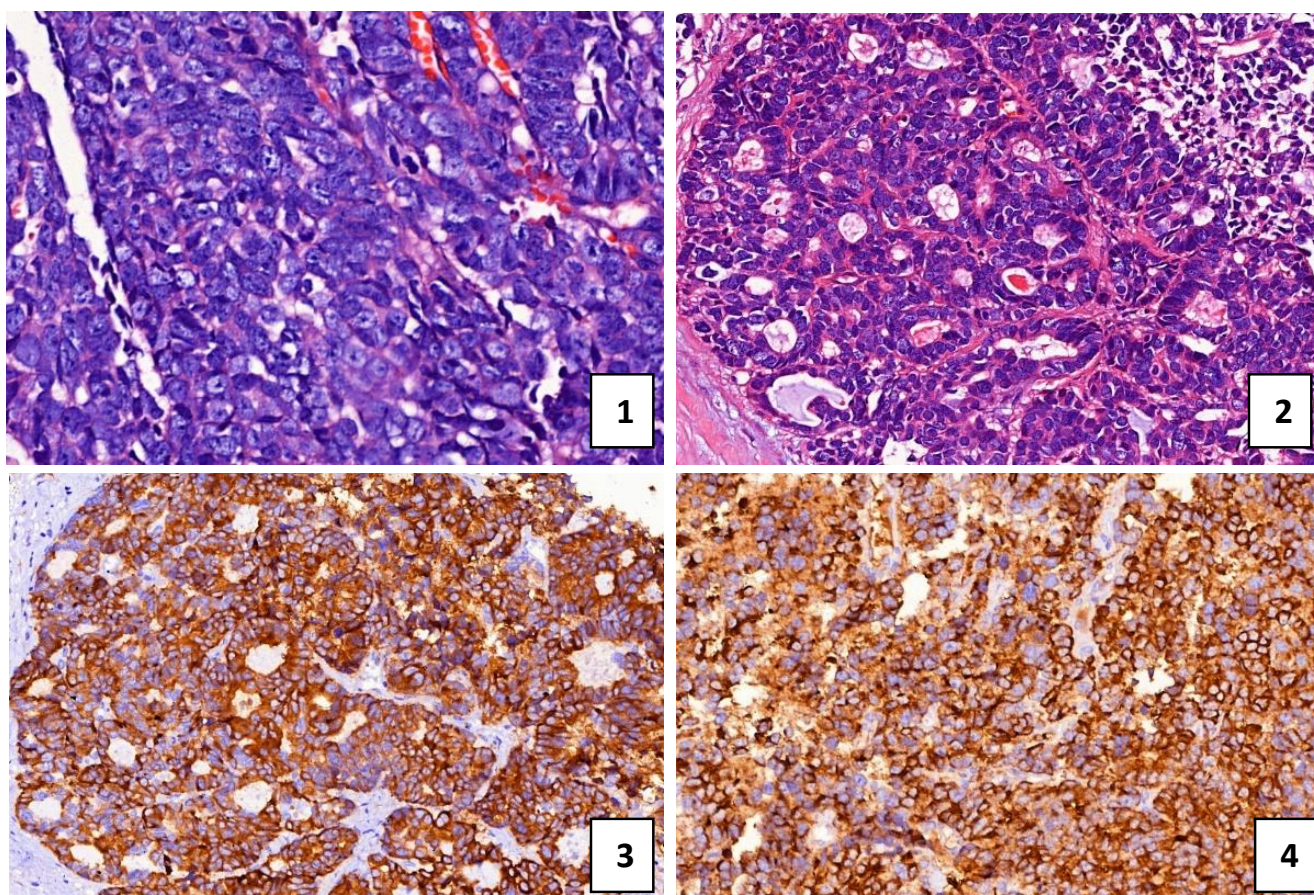
tumors and 2.1% of gallbladder tumors.<sup>3</sup> We report a case of neuroendocrine carcinoma of the gallbladder with a review of the literature.

### # CASE REPORT

A 76-year female presented to the surgery OPD with complaints of pain in the right upper quadrant of the abdomen for 5 months. She described the pain as sharp and colicky with radiation to the back. She had no history of fever, nausea, or vomiting. On examination, her abdomen was soft and non-distended with no tenderness in the right upper quadrant. Ultrasonography of the abdomen revealed a gallbladder calculus measuring 2cm in maximum dimension with sludge. Her complete blood count showed a raised total leukocyte count ( $14,850/\text{mm}^3$ ) with neutrophils constituting 78%, and normocytic normochromic anemia. Her liver function test was normal. She was admitted with the diagnosis of acute calculus cholecystitis. The patient was planned for a laparoscopic cholecystectomy, which was later converted to open surgery as there were adhesions of the gallbladder to the stomach, duodenum, and omentum. Intraoperative findings included the presence of a 3x2 cm single calculi with pus filling the entire gallbladder cavity. The patient underwent partial cholecystectomy with the

gallbladder partially removed in multiple fragments and a drain was placed. The pus was sent for microbiological examination which showed heavy growth of *Escherichia coli*. The patient was managed with antibiotics per the culture and sensitivity report and the drain was removed on the 4<sup>th</sup> post-operative day.

The gross specimen of the gallbladder was received in the histopathology laboratory. The specimen was submitted in multiple fragments, the specimen could not be oriented. The gallbladder mucosa appeared atrophic. The entire specimen was submitted for further processing. The microscopy of the slides showed a tumor infiltrating the entire thickness of the tissue. The tumor cells were arranged in nests, sheets, and tubules. The individual tumor cells showed moderate to marked pleomorphism and were intermediate to large. They had a high nuclear-to-cytoplasmic ratio with stippled chromatin and inconspicuous nucleoli. Mitosis was noted at 14/10 high power fields. Interspersed areas of necrosis were present. The overlying mucosa appeared denuded. Immunohistochemistry was positive for synaptophysin and chromogranin. Hence, the diagnosis was large cell neuroendocrine carcinoma. The patient and family were counseled regarding the treatment options and prognosis and they opted for palliative care.



**Figure 1:** Tumor cells arranged in sheets (H and E stain, 400x) **Figure 2:** Tumor cells arranged in an acinar pattern (H and E stain, 200x) **Figure 3:** Synaptophysin (200x) **Figure 4:** Chromogranin (200x)



## DISCUSSION

The 5<sup>th</sup> edition of the WHO Classification of Digestive System Tumors now adopts a uniform classification of the NEN throughout the entire gastrointestinal tract and hepatopancreatobiliary organs. It categorizes NEN as neuroendocrine tumors (grades 1,2,3), large cell neuroendocrine carcinoma, small cell neuroendocrine carcinoma, and mixed neuroendocrine- non-neuroendocrine neoplasms (MiNEN). The term carcinoid tumor has been discontinued. The classification and grading of the tumor are based on the mitotic rate and the Ki-67 proliferation index.<sup>4</sup> The morphological classification of these NEN has a genetic, clinical, epidemiological, histological, and prognostic significance.<sup>1</sup>

Gall bladder NEN occurs commonly in women and the common presenting symptoms are non-specific, including cholecystitis-like symptoms of abdominal pain, distension, and nausea.<sup>2</sup> The majority of patients do not have carcinoid symptoms as most gallbladder and extrahepatic duct NEN are non-functional amine precursor uptake and decarboxylation tumors.<sup>1</sup>

The mucosa of the gallbladder lacks neuroendocrine cells, hence the pathogenesis of gallbladder NEN has various theories. A widely accepted theory refers to the presence of long-term chronic inflammation from cholelithiasis leading to intestinal or pyloric metaplasia of the gallbladder mucosa. In advanced stages, the metaplasia is accompanied by the expression of neuroendocrine cells, the development of dysplasia, and ultimately malignant transformation.<sup>1,5</sup> However, not all NEN are associated with cholecystitis, but up to 92% of the cases have concurrent cholelithiasis.<sup>6</sup> Another theory consists of the differentiation of gallbladder stem cells into neuroendocrine cells. There is also a concept of gallbladder adenocarcinoma function switching to a neuroendocrine one, which may lead to the development of MiNEN.<sup>1</sup>

Recently, many studies have provided insights into the molecular mechanism of the development of NEN. The activation of epidermal growth factor receptor (EGFR) leading to the stimulation of downstream pathways, especially the protein kinase B is known to be one of the molecular mechanisms. The role of mTOR protein kinase is also under study.<sup>7</sup> Another study highlights the role of vascular endothelial growth factor receptor (VEGF). NENs have a rich vascular network with well-differentiated tumors showing dense vascular networks as compared to poorly differentiated NENs. This finding was termed the “neuroendocrine paradox” as angiogenesis is one of the hallmarks of malignancy and aggressiveness. Trials show increased clinical benefits and survival in NEN patients treated with anti-VEGF.<sup>8</sup> However, further studies diving into the details of the mechanism, validation of biomarkers, selection of patients, and predictors of response are still required.

The clinical features of gallbladder NEN overlap with those of cholecystitis and adenocarcinoma, hence the pre-operative diagnosis relies on a multi-modality approach. Imaging techniques like ultrasonography, CT scan, and MRI reveal a thickened gallbladder wall or a mass in the gallbladder fossa. These modalities are not able to distinguish between adenocarcinoma and NEN, however, they can locate suspected metastatic deposits and lymph node involvement.<sup>9,10</sup> The combination of ultrasonography with fine needle aspiration cytology increases the pre-operative sensitivity by 74-90% as compared to ultrasonography alone with a sensitivity of 44%.<sup>10</sup> Tumor markers like CA-19.9, CEA and CA-125 are negative.<sup>1</sup> The gold standard for diagnosis is histopathology with immunohistochemistry (IHC). Commonly used IHC markers include chromogranin A, synaptophysin, and neuron-specific enolase (NSE). These markers have a higher specificity for diagnosing NEN.<sup>1,9</sup>

Surgical resection is the treatment of choice in gallbladder NEN, which may include cholecystectomy alone or extended resection including part or lobe of the liver and lymph nodes. Re-exploration for incidental finding of gallbladder NEN during cholecystectomy shows residual disease in 74% of the patients.<sup>10</sup> Gallbladder neuroendocrine carcinoma is more aggressive with increased rates of lymph node metastasis; hence radical resection is opted for in these cases. For patients not suited for surgery, chemotherapy is an option that prolongs the survival period. However, there are no current standard protocols for gallbladder neuroendocrine carcinomas. Various molecular-targeted therapies are in trial.<sup>1</sup>

The prognosis of gallbladder neuroendocrine carcinoma is poor. These tumors are aggressive with lymph node metastasis and liver involvement at an earlier onset.<sup>1</sup> Liu et al reported that untreated cases died after 3 months and patients who underwent surgery and chemotherapy survived longer.<sup>9</sup> A 10-year study conducted by Duffy et al<sup>11</sup> found that patients with gallbladder neuroendocrine carcinoma had a median survival period of 9.8 months as compared to those with adenocarcinoma of the gallbladder with a median survival period of 10.3 months.

## CONCLUSIONS

Gallbladder neuroendocrine carcinoma is a rare neoplasm that is difficult to diagnose preoperatively as the clinical symptoms and imaging findings overlap with those of cholecystitis and other carcinomas of the gallbladder. The gold standard for diagnosis is histopathology with immunohistochemistry. These tumors are aggressive with early metastasis and poor patient survival. The molecular mechanisms and pathogenesis require further research which may open doors to treatment options for targeted therapy and improve the overall prognosis. Owing to the low incidence of this tumor, a standard management protocol has not been developed. A multi-institutional effort to formulate a protocol for the management of the patient is recommended.

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