Case Report

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High Grade Neuroendocrine Carcinoma of the Gall Bladder: A Rare Entity

Surgical Oncology Section

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ABSTRACT

Primary neuroendocrine carcinoma of the gall bladder (GB) is an extremely rare condition and is usually an incidental diagnosis. Here, we describe a rare case of primary gall bladder neuroendocrine carcinoma in a 30 year old lady who presented with upper abdominal pain and palpable lump in the right hypochondrium. Computed tomography of the abdomen showed an ill-defined heterogeneous soft tissue mass involving gall bladder and adjacent liver parenchyma with no obvious regional adenopathy. Metastatic work-up was normal and the patient underwent radical cholecystectomy. Histopathology and immunohistochemistry (IHC) study revealed high grade neuroendocrine carcinoma of the gall bladder involving the adjacent hepatic parenchyma. However, there was no evidence of clinical endocrinopathy. Patient received adjuvant chemotherapy and is disease free at 14 months of follow up.

The present case emphasizes the need for better detection, evaluation and analysis of such rare entities, to identify their natural course and effective treatment modalities.

Keywords: Gall bladder, Liver, Neuroendocrine tumor

CASE REPORT

A 30-year-old woman was admitted with a 7 month history of dull pain and mass in the right upper abdomen. No other significant history was noted. On general examination, she was well built and nourished with no jaundice, or lymphadenopathy. Abdominal examination revealed palpable gall bladder mass in right hypochondrium, mild hepatomegaly and no ascitis.

Laboratory investigation revealed normal haematological findings and Liver function tests were within normal limits. Tumour markers (Carcinoembryonic antigen [CEA], CA 19-9 and Alpha fetoprotein [AFP]) were within normal limits.

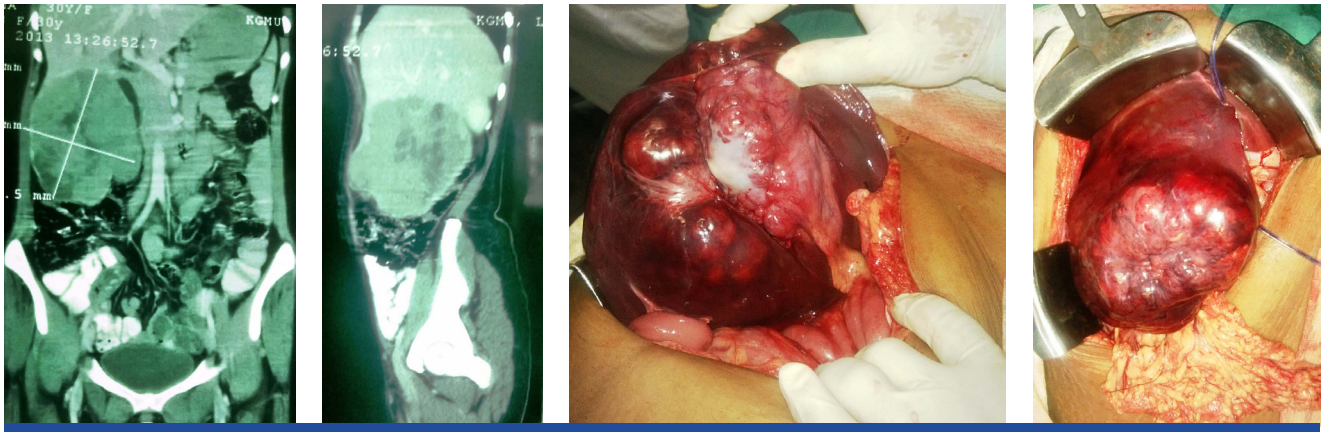
Contrast-enhanced computed tomography (CECT) of abdomen and pelvis revealed an ill-defined heterogeneous mass of 8 x 6cm with foci of necrosis which appeared to arise from the fundus and body of the gallbladder with involvement of adjacent hepatic parenchyma. No biliary dilatation and regional adenopathy were noted [Table/Fig-1a,b]. Ultrasound guided FNAC of gall bladder mass revealed poorly differentiated adenocarcinoma. Chest X-ray was normal.

With a preoperative diagnosis of gallbladder carcinoma, the patient was planned for exploratory laparotomy. At laparotomy, a large, bosselated, highly vascular mass was found arising mainly from fundus of the gallbladder with involvement of adjacent liver parenchyma [Table/Fig-2a,b]. No regional or distant metastasis noted. Patient underwent radical cholecystectomy.

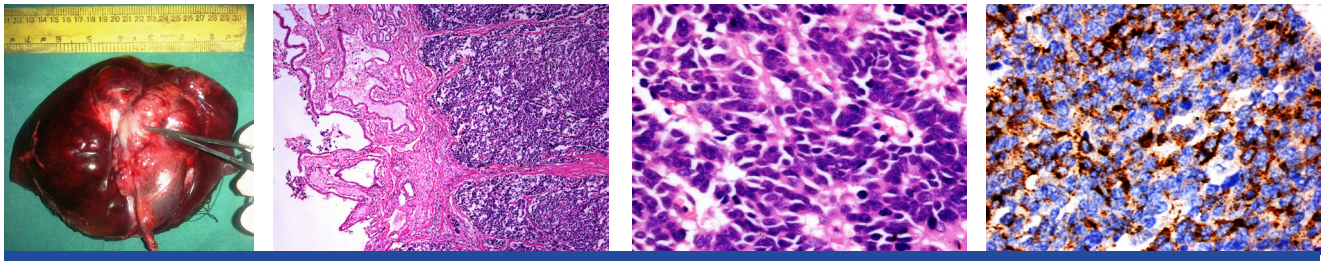
Pathological findings on gross examination revealed a growth measuring 9 × 7.5 cm involving the body and fundus of gall bladder and extending into adjacent liver parenchyma [Table/Fig-3]. Resection margins of gall bladder and liver were clear.

Histologically, the tumor was seen involving full thickness of the gall bladder wall (level of invasion up to serosa), and liver parenchyma with uninvolved regional nodes. Tumor consisted of diffuse sheets, nests and focal acinar pattern of small to medium sized, round cells having high nucleo-cytoplasmic ratio, pleomorphic nuclei with speckled chromatin and scanty cytoplasm. Tumour showed moderate pleomorphism with mitotic figures (>30/10HPFs) and foci of necrosis were evident [Table/Fig-4a,b]. No definite evidence of vascular permeation, perineural invasion or lymphatic permeation was seen. In view of small cell nature of the lesion, immunohistochemistry (IHC) was done for characterisation.

Immunohistochemical studies revealed that the tumor cells were strongly positive for chromogranin A [Table/Fig-5] and synaptophysin with focal positivity for cytokeratin 7. A possibility of lymphoma was excluded by negative staining on leucocyte common antigen (LCA). Postoperative course was uneventful. Patient received adjuvant chemotherapy (6 cycles of cisplatin and etoposide. Patient is disease free, 14 months after completion of treatment.



[Table/Fig-1a & b]: Computed tomography showed an ill-defined heterogeneous mass arising from the fundus and body of the gallbladder with involvement of adjacent hepatic parenchyma **[Table/Fig-2a & b]:** Laparotomy revealed a highly vascular, bosselated mass was found arising mainly from fundus of the gallbladder and involving adjacent liver parenchyma



[Table/Fig-3]: Specimen showed a growth involving the body and fundus of gall bladder and adjacent liver parenchyma **[Table/Fig-4a]:** Microscopy revealed the tumor cells invading the gall bladder wall and liver parenchyma **[Table/Fig-4b]:** Hematoxylin-and-eosin section showed sheets of small round cells with prominent nucleoli, and coarse "salt and pepper" chromatin., **[Table/Fig-5]:** Tumor cells stained positive for chromogranin

DISCUSSION

Primary neuroendocrine carcinoma of the gall bladder (GB) is an unusual entity. It accounts for 0.2% of all neuroendocrine tumors [1]. Neuroendocrine tumours are classified as classical carcinoid tumour (secretory) and atypical carcinoid or small cell carcinoma (non secretory). More than 50% of the cases of GB carcinoids reported in the literature are usually non secretory variety. Classical GB carcinoids are rarely metastatic and invasive in nature, while atypical or small cell variety is often aggressive and has a dismal prognosis [2]. Non secretory tumours usually present with symptoms due to local disease and distant metastasis, whereas secretory tumours produce symptoms related to secretory peptides.

The term "Neuroendocrine tumors" (NETs) are unusual epithelial neoplasm's with predominant neuroendocrine differentiation [3]. Majority of NETs occur in the gastrointestinal and respiratory tract. Primary Gall bladder neuroendocrine tumors (GB NETs) are extremely uncommon. The first case of GB NET was described by Joel in 1929 and till date very few cases are noted in the literature [4]. According to Sanders, there were only seven cases of Gall bladder NETs reported among 3633 digestive tract NETs accounting for 0.2%, while only one case of Gall bladder NETs was described among 2837 digestive NETs (0.04%) as per a study by Godwin [5].

Neuroendocrine cells were initially thought to arise from neural crest cells, but are now proven to be derived from local multipotent gastrointestinal stem cells. GB NETs may also arise from endocrine cells induced by intestinal metaplasia of the body and fundus as well as from pre-existing endocrine cells in the neck of gall bladder [6]. Genetic factors play a vital role in the oncogenesis and progression of these tumors.

Based on review of literature, the age of the patients ranges from 38 to 81 years with a marked female predominance [7]. Clinical features of neuroendocrine tumors are similar to gall bladder carcinoma. Most common presenting symptom is vague abdominal pain or discomfort and may be associated with cholelithiasis. Majority of cases are asymptomatic. Radiologic features are non specific and often mimicks carcinoma gall bladder. Preoperative diagnosis of NETs is very difficult and usually misdiagnosed as carcinoma gall bladder . In the present case, imaging showed mass in gall bladder, but determination of histological type of tumor and features to differentiate from gall bladder carcinoma is often difficult. Most cases of GB NETs remain localised and only 11 to 15% of patient were found with distant metastasis [7].

Most GB NETs were diagnosed incidentally on immunohistological examination of gallbladder specimen at autopsy following surgical treatment for cholecystitis or in

whom malignancy was suspected. Grading of tumor refers to the biologic aggressive behaviour of the tumor. Low grade NETs have indolent course, high grade tumors are usually aggressive, whereas intermediate grade NETs are moderately aggressive and have a less predictable course. The term 'Well differentiated NETs" refers to low and intermediate grade tumors, whereas poorly differentiated tumors include high grade tumors. Based on histological analysis, Soga revealed that 100% of well differentiated NETs stain positive for Chromogranin and 93.8% for neuron specific enolase [8].

GB NETs should be treated with a multidisciplinary approach comprimising of surgery, chemotherapy and receptor radio nucleotide therapy. Surgical treatment includes simple/radical cholecystectomy with regional lymphadenectomy and even extensive hepatic resection in order to obtain negative margin, based on the size and stage of the lesion [9].

Role of chemotherapy in GB NETs is still debatable and has a role in metastatic setting with minimal efficacy. Chemotherapeutic agents including cisplatin, 5-fluorouracil, etoposide, and doxorubicin have limited role and are commonly used in poorly differentiated GB NETs. Receptor radiotherapy also termed as Biotherapy using somatostatin analogues (octreotide or lanreotide) is a promising treatment modality for patients with metastatic disease, in whom other modalities have minimal role [10, 11].

Based on data analysed by Soga from the international sources (138 cases of primary GB NETs), cumulative 5 year survival rate was 60.4% [8]. According to SEER data (1992-99), 5 year survival rate for GB NETs is 58.8 + 13.3% [12]. Modlin and colleagues reported a median survival of 9.8 months among 278 patients of GB NETs [12]. Specific prognostic factors of GB NETs include tumor size, grade, depth of invasion and regional/distant metastasis. Hence it is important to diagnose tumor at an early stage and perform definitive surgery as early as possible to improve the prognosis of neuroendocrine tumors.

CONCLUSION

Neuroendocrine carcinoma of the gall bladder is rare condition with poor prognosis. Exact aetiology is not known. It is often difficult to differentiate from GB carcinoma based on clinical presentation and radiological investigation. It is usually diagnosed postoperatively based on histological findings. Surgery is the mainstay of treatment with ill-defined role of chemo-radiotherapy with poor outcome. We present this case to highlight the rarity of this entity and utility of immunohistochemistry analysis.

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