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Rare Case of Metastatic Gall Bladder Neuroendocrine Carcinoma: A Case Report

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Abstract
Neuroendocrine tumours (NET) of the gallbladder (GB) are nonspecific in nature. The diagnosis is usually made after cholecystectomy for cholelithiasis. The main treatment option is surgery. The role of adjuvant therapy after complete resection is undefined, whereas in metastatic disease, chemotherapeutic drugs have shown some activity. Here, we report the case of a 65 year old female who was presented to the hospital with swelling in the left neck and back pain radiating to chest. Fine Needle Aspiration (FNA) of left supraclavicular lymph node done showed poorly differentiated carcinoma with neuroendocrine features. Subsequent Contrast Enhanced Computed Tomography (CECT) imaging was suggestive of GB malignancy along with extensive lymph node metastasis. Positron emission tomography (PET) scan confirmed the gall bladder malignancy with extensive lymph node metastasis. Six cycles of chemotherapy with Cisplatin and Etoposide was given with the diagnosis of metastatic GB-NET, for which she received partial response.
Keywords: *Neuroendocrine tumour (NET), Gall bladder (GB), Positron Emission Therapy (PET).*

Introduction

Neuroendocrine carcinomas (NECs), also referred to as amine precursor uptake decarboxylation (AUPD) tumours, accounts for <1% of all major malignant tumours. They initiate from the disseminated neuroendocrine cells. Gastrointestinal tumours account for 66% (mainly found in rectum, pancreas, ileum and jejunum) and respiratory tract tumours account for 31% of NECs[1]. However, gall bladder (GB) NEC is very rare[2]. A previous report showed NECs occurring at the extra hepatic duct (0.2%-2%) and GB (0.2%) of all NECs of the gastrointestinal tract[3]. The first carcinoid tumour was described in 1888, while the first carcinoid tumour of GB was reported in 1929. These tumours are usually diagnosed at an advanced stage having a very aggressive biological behaviour. There are no specific signs or symptoms for this group of tumours and the diagnosis is usually incidental,

made during surgery for a suspected gallstone-related disease. We herein describe the case of a GB-NEC with nodal metastasis in a 65 year-old woman.

Case Report

A 65 year old female presented to the hospital with complaints of intermittent episodes of back pain radiating to chest of six months duration. Three months later, she noticed a swelling on the left side of her neck and also had loss of appetite and significant weight loss. She has been on regular medication for Systemic hypertension and Diabetes Mellitus for the last five years. She had undergone hysterectomy with bilateral salphingo-ophorectomy in 2002 for dysfunctional uterine bleeding and bilateral cataract surgery in 2012.

On physical examination there were multiple cervical lymph nodes. Ultrasonography of the neck and thyroid showed enlarged left supraclavicular lymph node and Left Level V lymph nodes.FNA of left supraclavicular lymph node showed poorly differentiated carcinoma with neuroendocrine features. CECT Brain, neck, chest and abdomen showed an ill-defined enhancing mass in the gall bladder suggestive of gall bladder malignancy along with cervical, mediastinal and abdominopelvic lymphadenopathy.

Biopsy from left supraclavicular lymph node was performed. Histopathological examination showed poorly differentiated carcinoma with capsular invasion. MIB -1 index (Ki-67) was 60-65%. Immunohistochemistry (IHC) revealed expression of synaptophysin and chromogranin (diffuse strong positivity) and TTF-1 was negative. Histopathology and IHC confirmed the presence of a metastatic poorly differentiated neuroendocrine carcinoma.

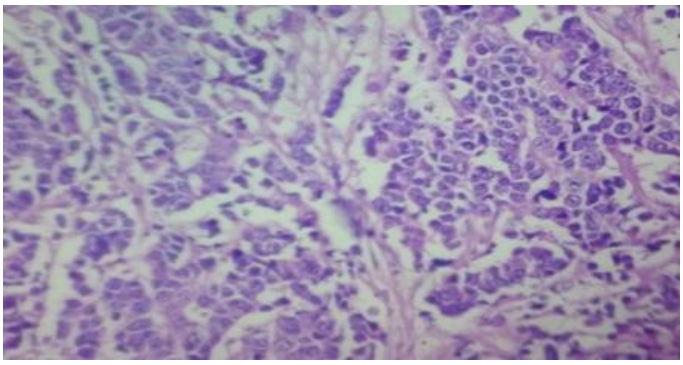

Figure 1 Nests and cords of cells with moderate cytoplasm and round to oval nuclei with granular chromatin.

Figure 2 IHC showing chromogranin diffuse strong positivity

PET findings were of an extensive metastatic disease with mass lesion in the GB along with metabolically active left cervical, mediastinal, right hilar and abdomino-pelvic lymphadenopathy.

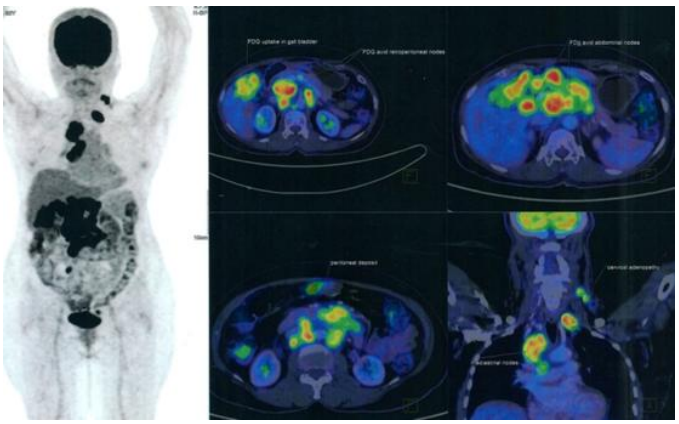

Figure 3 Abnormal areas of FDG uptake in level V SUV 12.59, Left supraclavicular lymph node SUV 14.24, Right upper Para tracheal lymph node SUV 14.98, Carinal lymph node SUV 14.74, Right hilar node SUV 15.24, Gall bladder SUV 11.83, Portocaval SUV 15.95, Peripancreatic SUV 16.30, Periportal SUV 16.62, Aortocaval

SUV12.76, Para aortic SUV 13.84, Precaval SUV 16.23, Left common iliac SUV 10.82, Peritoneal deposits SUV 11.89, Peri pyloric region SUV 10.94.SUV-Standardized Uptake values.

Surgical oncology consultation was taken and planned gall bladder biopsy, but patient deferred. Also advised serum chromogranin assay, but the patient was not willing for the same

A clinical diagnosis of GB-NEC with extensive nodal dissemination was made taking into account the clinical, radiological and histological features.

After a thorough discussion with patient and relatives, regarding the stage of the disease, prognosis, available treatment options, expected outcome and toxicity of treatment, it was decided to start her on chemotherapy with a palliative intent. Chemotherapy regimen consisted of Cisplatin 80 mg IV (for one day) and Etoposide 150mg (for 3 days) repeated every 3 weeks for six cycles. PET scan after completion of 6 cycles of chemotherapy showed partial tumoral response. Since she was clinically asymptomatic after 6 cycles, it was decided to stop chemotherapy and to keep her on follow up once every 3 months .She had disease progression after 3 months and she expired after 4 months of completion of chemotherapy.

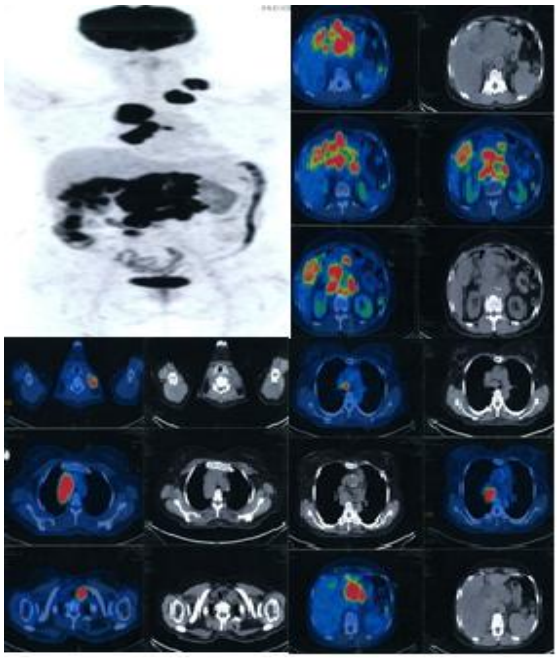

Figure 4 Abnormal areas of FDG uptake in Omentum SUV 8.25, Peri pancreatic lymph node SUV 7.85, Gall bladder SUV 5.34, left Level V, SUV 8.81,Left supraclavicular lymph node SUV 8.43,Right Para tracheal lymph node SUV 8.73, Precarinal lymph node SUV 8.33, Right hilar lymph node SUV 8.71, Para aortic lymph node SUV 7.09 (Post 6 cycles chemotherapy)

Discussion

Neuroendocrine cells are generally found in the intestinal or gastric metaplastic GB mucosa and are absent in GB. Primary GB-NETs are very rare. In case of Surveillance, Epidemiology and End Results (SEER) Program registry (1973-2005), only 278 cases were reported, which accounted for 0.5% of all NETs and 2.1% of all GB cancers [4]. Based on this report, in the US, GB NET incidence accounted for 0.2-0.3/100.000. A retrospective study involving 25 GB-NETs showed that females were affected more (68%) who were aged between 26 and 79 years[5].

Another study confirmed derivation of neuroendocrine cells from local multipotent gastrointestinal stem cells, which scraped the older notion where it was thought that the cells migrated from neural crest[6]. Neuroendocrine cells are absent in GB mucosa. However, GB mucosa that are marked with intestinal or gastric metaplasia, secondary to chronic inflammation because of the cholelithiasis, shows presentation of various types of neuroendocrine cells.

Imaging modalities widely used in the diagnosis of NETs includes sonography, CT, MRI, positron emission tomography [F] - fluorodeoxyglucose (FDG) and somatostatin receptor scintigraphy (SRS). PET and CT shows more sensitivity compared to SRS. In addition to this, SRS cannot detect small tumours which are below 2 cm.

Serum chromogranin (CgA) levels were elevated in 60-80% of the patients diagnosed with NETs. In this case report, serum CgA levels was not measured because of the unwillingness of the patient.

The patients with high proliferation index should receive chemotherapy, while patients with low proliferation index can be treated with

somatostatin analogues and interferon (IFN).In our case, MIB-1 index was 60-65%.

En bloc surgical resection is the only treatment option for GB-NECs, which includes clearing the localized lymph nodes and hepatic lobectomy.

GB-NET being a very rare disease form, we have limited knowledge on its tumour biology. Apart from surgery, radiotherapy and chemotherapy are also other options for treating these tumours.

The first line chemotherapeutic agents used are cisplatin/carboplatin and etoposide[7].

Conclusions

GB-NEC is a special type of gallbladder carcinoma with low incidence rate, which has no typical clinical presentation. Imaging, pathological and immunohistochemical examinations are needed for definite diagnosis. However, with a very low incidence and only few studies focused on this disease, no universally accepted treatment is available.

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