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A metastatic neuroendocrine small cell carcinoma of the gall bladder: case report and a comprehensive review of the literatures

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Abstract
Primary neuroendocrine small cell carcinoma (SCC) of the gallbladder (GB) is a rare, aggressive malignancy accounting for less than 1% of all GB tumours. With a high propensity for extensive local invasion and early metastasis, the disease carries a poor prognosis without prompt intervention. Definitive diagnosis requires histopathological examination (HPE) with immunohistochemistry (IHC). Here, we report a metastatic case of SCC-GB and review the literature of metastatic SCC GB.

Keywords: Neuroendocrine tumours, Small cell carcinoma of Gallbladder, Metastasis, neuron-specific enolase (NSE), Synaptophysin, Chemo responsive.

Introduction
Neuroendocrine tumours (NET), which account for <1% of all malignant tumours, originate from the disseminated neuroendocrine cells in the body. Most NETs occur in the gastrointestinal tract (GIT) and the respiratory tract. NETs in the GIT are mostly found in the appendix, rectum, jejuno-ileum, and pancreas. The primary NET of the GB is a rare disease, accounting for 2% of all GB tumours, 1.4% of all GIT-NETs, and 0.5% of all NETs (1). We report a case of chemo responsive metastatic GB NET-SCC type in a 52-year-old man presenting with ascites, extensive lymphadenopathy followed by a pertinent literature review of metastatic GB NET-SCC type.

A 52-year-old, non-smoker, and non-alcoholic male presented with painful distended abdominal, dyspnoea, and loss of appetite for 1 month. On examination, he had tense ascites, decreased bilateral breath sounds, and enlarged left supraclavicular node. Initial routine blood investigations were normal. Ascitic and pleural fluid cytology was positive for poorly differentiated malignancy. Ultrasound of the abdomen showed an ill-defined lesion of 5.0*4.7cm size in segment IV of liver inseparable from GB, gross ascites, bilateral moderate pleural effusion, omental and peritoneal deposits. Further on Computed tomography (CT) evaluation, revealed eccentric nodular polypoidal GB mass with the thickened wall in fundus, body and neck region, the gross dimension of 68*56*37 mm, and loss of fat plane from adjoining segment V and IVB hepatic parenchyma was suggestive of Gallbladder carcinoma. Focal extrinsic compression with indentation of the common hepatic duct and luminal narrowing was also found. Extensive peritoneal and omental carcinomatosis with gross ascites, bilateral pleural effusion with lower lobe atelectasis, and multiple bulky matted porta-hepatis, portocaval, peripancreatic, epicardial and paracardial necrotic nodes suggesting a possibility of an aggressive, metastatic GB malignancy (Figure 1A)

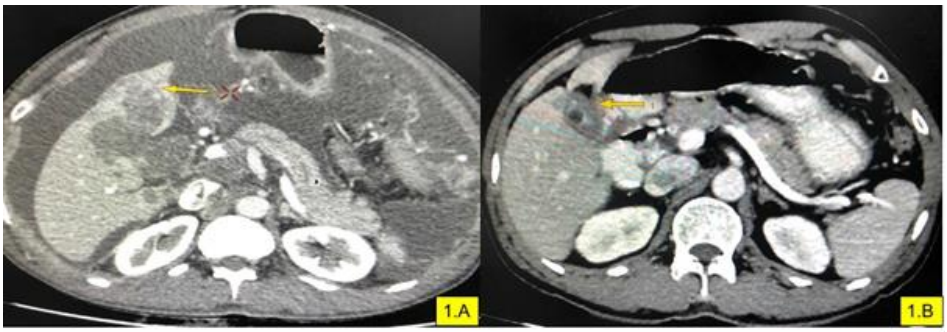

Fig 1:

a. CT scan of Abdomen(axial plane) : Eccentric mass with thickened wall fundus, body and neck region of gall bladder (yellow arrow), gross dimension of 68*56*37 mm shows loss of fat plane from adjoining segment V and IVB hepatic parenchyma, suggestive of Gallbladder carcinoma (Pre-chemotherapy), gross ascites , multiple matted intra-abdominal nodes.
b. Post Chemotherapy response assessment in CT Abdomen shows reduction in the size of primary GB lesion (yellow arrow) along with resolution of ascites, pleural effusion, peritoneal deposits, omental thickening, and periportal lymph node

Excisional biopsy of the left supraclavicular node was done. The histomorphology showed the complete effacement of lymph node architecture. Tumour cells were arranged in cords, sheets, nests, and pseudo-rosettoid pattern with increased mitotic figures(Figure 2A). It also had caseating granulomatous inflammation at the periphery with foci of extracapsular tumour emboli. The cell was small round hyperchromatic nuclei with scant cytoplasm(Figure 2 B).

With a provisional diagnosis of metastatic poorly differentiated carcinoma of small cell type, a panel of Immunohistochemistry (IHC) markers was designed to rule out close differentials. IHC was strongly positive for neuron-specific enolase (NSE), synaptophysin (Figure 3 A & B); and negative for CK7 (cytokeratin 7), CEA (carcino embryogenic antigen), TTF1. The final diagnosis was metastatic Neuroendocrine tumour of Gallbladder, the small cell type of carcinoma (NET- SCC type).

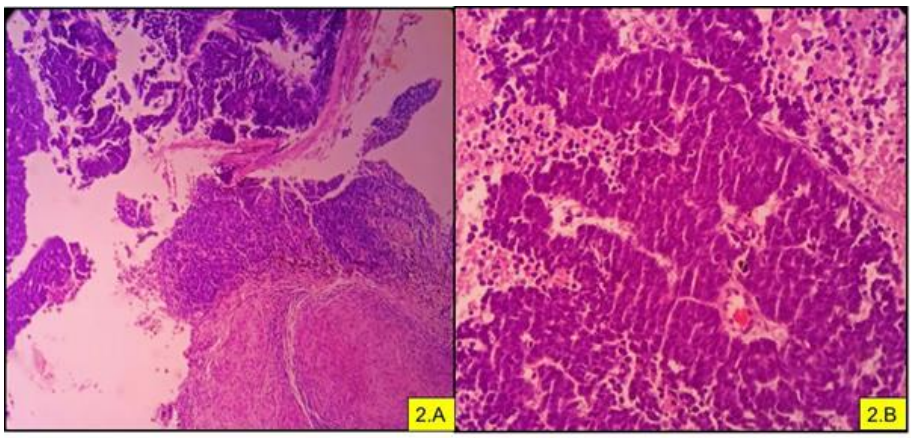

Fig 2

a. Photomicrograph show small cell carcinomatous deposit (above) arranged as nests along with small foci of epithelioid granuloma (below) beneath the capsule.(H&E, 10x).
b. Photomicrograph show small ovoid to spindle shaped hyperchromatic cells with brisk mitosis arranged in broad trabeculae surrounded by necrosis and lymphocytes. (H&E, 40x).

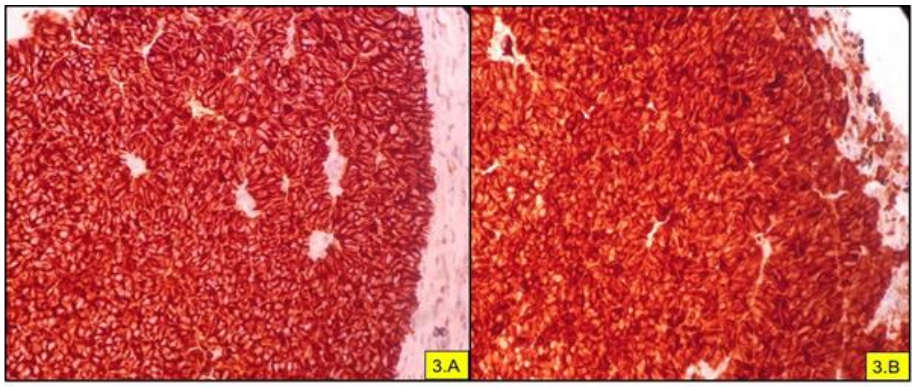

Fig 3

Tumour cells show strong synaptophysin positivity (IHC, 40x).
Tumour cells show strong NSE positivity (IHC, 40x).

He was started on chemotherapy with etoposide and cisplatin. Post 4 cycles of chemotherapy, response assessment showed a reduction in the size of primary GB lesion along with the resolution of ascites, pleural effusion, peritoneal deposits, omental thickening, and periportal lymph nodes (Figure 1 B). At present, he has completed 6
cycles of chemotherapy and is doing well.

Discussion

Primary NETs are a distinct group of tumours with characteristic histologic features. They can occur at any site in the body where enterochromaffin cells are present, especially GIT and respiratory tract being the most common sites. Among the GIT-NETs, GB is a rare site of occurrence, accounting for 1.4% of all GIT-NETs (1).

Small cell carcinoma (SCC) is a clinicopathologic entity that usually arises in the lung but can also originate in a wide range of extrapulmonary sites such as GIT, urinary bladder, and prostate. Extrapulmonary SCC (ESCC) are rare and have an aggressive natural history characterized by early and widespread metastases. After its first description in 1981(2), over 100 cases of GB-SCC have been reported in the literature, which accounts for 0.5% of all GB malignancies (1). As there are no neuroectodermal cells in the GB mucosa, few investigators postulated that SCC arises from epithelial metaplasia secondary to cholelithiasis and chronic cholecystitis. Novel research methods in the pathogenesis demonstrate the role of epidermal growth factor receptor, protein kinase B, a target protein of rapamycin, and extracellular signals that regulate kinase expression (3).

The details regarding published case reports and case series of metastatic SCC-GB are tabulated. (Table 1). Our patient presented with gall bladder mass, ascites, weight loss, and supraclavicular lymphadenopathy mimicking the classical adenocarcinoma of the gall bladder. According to the published literature, SCC is more common in elderly women. Clinical presentation varies among patients and includes vague upper abdominal pain, jaundice, weight loss, bleeding, and an incidental finding of a large tumour mass indistinguishable from other tumours arising from GB (1,4). Functionally they can be no secretory, secretory, and metastatic (5). These are usually large tumour with extensive necrosis, have diffuse growth pattern that mostly involves the submucosa. Poorly differentiated NETs grow in sheets and cords and have cells with irregular nuclei, inconspicuous nucleoli, cytoplasmic neurosecretory granules along with high mitotic index (3,6). SCC typically express neuron-specific enolase (NSE), while some express synaptophysin, chromogranin, cytokeratin, and Leu-7(7). Owing to the aggressive behaviour, they are often discovered late in the disease process when adjacent organ systems are invaded or the biliary tract gets obstructed. Metastasis is seen in the majority of cases to the lymph nodes, liver, lung, and peritoneum which is an indication of poor prognosis(3,8).

No standard of care exists for treating GB SCC. The benefit of chemoradiation, chemotherapy, or radical surgery remains unclear and has not been standardized in metastatic SCC of GB (3,9). It tends to be highly invasive and develops early with lymph node metastasis. Surgery followed by radiotherapy and chemotherapy is recommended to prolong the survival period of such patients. The various chemotherapy regimens used include platinum-based agents-cisplatin, carboplatin with or without etoposide, and 5-FU(4,8,10). Despite any modality of treatment, prognosis remains poor with overall survival ranging from 2.5-31.5 months (5,11). This case is reported for its rarity and to convey the importance of detailed pathological examination of tissue even in cases which may clinically and radiologically look very obvious.

Table 1: Details regarding published cases of metastatic small cell carcinoma of gall bladder

S.NO.	Study, Year	Number, n		Gender	Age	Sites	Treatment	Survival (months)
		Total	Metastasis					
1	Carrera *et al**. 2015 (*review of all publishe d cases from 1984-2014)* [8].	53	34	F-68% (23)	61.5 (32-89)	Liver-88.2% LN- 70.5% Multiple sites-64.7%	Chemotherapy-50% (17) a) P+E-41% (7) b) P+G-12%(2) c) 5FU-12% (2) d)Others-35% (6) Radiotherapy- 5.8% (2)	9.1
2	Yun *Et al*. 2015 [11].	4	2	F-50% (1)	55.5	LN- 50% Mutilple sites- 50%	Chemotherapy (P+E) - 50% (1)	31.5
3	Kamboj *et al*. 2015 (4)	16	16	F-37. 5% (6)	54.3 (29-77)	Liver- 68.7 % LN- 68.7% Multiple sites- 75%	Chemotherapy- 62.5% (10) a) P+E- 80% (8) b) P+G- 20% (2)	4.3
4	Adachi *et al*. 2016 (12) [12].	1	1	F	79	Liver, LN	Not given	3.0
5	Elmhadi *et al*. 2017 (13)	1	1	F	49	Liver, LN, Bone	P+E	18

7	Zarog *et al*. 2018 (6) [6].	1	1	F	69	Liver, LN, Lung	P+E	7
8	Kumar *et al*. 2019 (5) [5].	1	1	F	61	Liver, LN	Not given	2.5
9	Hussain *et al*. (14) [14].	1	1	M	65	Liver, LN	P+E	9
10	Fujimoto *et al*. 2020 (15) [15].	1	1	F	68	Liver, LN	P+E	>16
11	Current case	1	1	M	52	LN	P+E	>6

LN- lymph nodes, P- Cisplatin/Carboplatin, E- Etoposide, G- Gemicitabine, 5FU- 5- Fluorouracil

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