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SMALL CELL CARCINOMA OF GALL BLADDER: A CASE SERIES AND REVIEW OF LITERATURE

Oncology

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ABSTRACT

Small cell carcinoma (SCC) of Gall Bladder (GB) is a rare malignancy with a very aggressive course. There is very little literature regarding this disease with mostly limited to case report and case series. Here we report a series of 3 cases of SCC of GB with varied clinical course and a brief review of literature regarding this rare disease.

KEYWORDS

Gall Bladder, Small Cell, IHC, Chemotherapy

INTRODUCTION:

Gall Bladder cancer (GBC) usually arises from epithelial lining of gall bladder (GB) and is the most common biliary tract cancer in the world. It usually presents as GB wall thickening or as a mass in GB (1). The incidence of GBC in India varies geographically with maximum cases reported in North and North east. It is twice more common in females as compared to males (2,3). The median age of presentation of GBC in females is 65 years (3).

According to the Surveillance Epidemiology End Results database 83% are adenocarcinomas and rest being papillary carcinoma, adenosquamous carcinoma, mucinous carcinoma and signet ring cell carcinoma (4).

Small cell Carcinoma (SCC) of lung comprises of 15% of all cancers, with extrapulmonary SCC has an incidence of 0.1-0.4%, they commonly occur in gastrointestinal tract or genitourinary tract but can affect any organ of the body (5). SCC of GB is very rare malignancy with aggressive course and reported incidence of 0.5% of all GBC (6). It was first reported by Albores-Saavedra in 1981 (7).

Here we report an institutional experience of 3 cases of SCC of GB with a review of literature regarding natural history, treatment and outcome of disease

Case Series:

Case 1:

A 83 year old female presented in Outpatient department (OPD) with complaints of pain in abdomen, with loss of appetite and weight loss not documented. On examination she was Eastern Co-operative oncology group (ECOG) performance status (PS) 1, with hepatomegaly rest of the examination was normal. Ultrasonography (USG) of abdomen revealed mass in GB with multiple hypoechoic lesion in both lobes of liver and largest being 3.5x4 cm. Blood parameters were within normal limit with sligh elevation of SGOT and SGPT. She underwent a contrast enhanced Computed tomography (CECT) scan of abdomen and pelvis which revealed a mass in GB of around 5.3x6 cm with multiple liver deposits in both lobes with portal adenopathy. She underwent USG guided biopsy from liver lesion and histopathology (HPE) was reported to be small round cell tumor possibility of neuroendocrine carcinoma. Immunohistochemistry (IHC) was done and was positive for synaptophysin, cytokeratin, chromogranin and ki67 was >90%. She was started on chemotherapy with Etoposide and Carboplatin, after 4 cycles of chemotherapy showed a good response to treatment and hence completed 6 cycles of the same. CECT scan after one month showed further reduction of disease and was kept on follow up. She came after 2 months with icterus, weight loss and vomiting and USG was suggestive of increasing lung nodules with GB mass and due to her poor PS, she was kept on best supportive care (BSC), she succumbed after few days.

Case2:

A 53-year-old female with no comorbidity presented in OPD with complaints of pain in abdomen mainly right side with loss of appetite, vomiting and weight loss for 2 months increased since past 15 days. On examination she was ECOG PS 1 with no other positive findings. USG abdomen was suggestive of mass in gall bladder encroaching liver. CECT abdomen showed a huge mass in GB with involvement of liver of size 6.5x6 cm rest of the scan was normal. She underwent biopsy from the liver part of GB mass and HPE was reported to fibrocollagenous tissue infiltrated by clusters of round-cell tumour with a high nuclear: cytoplasmic ratio. IHC was positive for synaptophysin, pan cytokeratin and ki-67 was >60%, hence a diagnosis of small cell carcinoma GB was made. She was started on chemotherapy with etoposide and cisplatin. She completed 6 cycles of therapy and CECT was suggestive of significant response with regression of mass and was advised for surgery, however, patient was lost to follow up.

She presented again after 5 months with the same complaints and CECT was showing a mass in gall bladder with multiple liver deposits and retroperitoneal lymph nodes (RPLN), she was re-challenged with etoposide and cisplatin and after 3 cycles showed good clinical response with reduction of symptoms and hence continued the same. After, 5 cycles her symptoms worsened and started having icterus and CECT was suggestive of progressive disease and she was started on second line therapy with topotecan. However, patient died after 1st cycle of therapy.

Case 3:

A 47-year-old female came with complaints of pain in epigastrium right hypochondrium for 1 month. Her physical examination was normal. USG and Magnetic resonance Imaging (MRI) of abdomen revealed a mass in gall balder of size 7.4x 6 cm with infiltration of segment IVb of liver. Rest of the work up was normal with slight elevation of alkaline phosphatase. She was taken up for surgery and underwent radical cholecystectomy with sub segmental resection of liver and HPE was suggestive of small round cell tumor and IHC was confirmatory of SCC with positive markers being Synaptophysin and Chromogranin. She received concurrent chemoradiotherapy with etoposide cisplatin followed by adjuvant chemotherapy for 3 cycles with the same regimen. Patient is currently on follow up and doing fine.

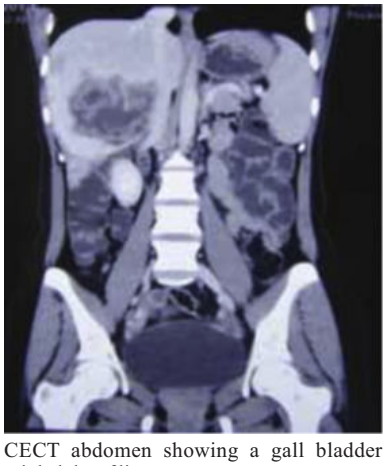
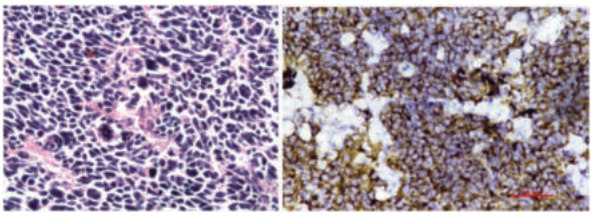


Figure 1: CECT abdomen showing a gall bladder mass with infiltration in right lobe of liver.



(a) (b)

Figure 2: (a) Microscopy showing abundant mitotic figures with apoptotic bodies and necrosis (b) IHC showing diffuse and strong staining for Synaptophysin

DISCUSSION:

Neuroendocrine neoplasms (NEN) can occur in any part of the body with most commonly affecting lung and GI tract. NEN of gall bladder is very rare and comprises around 0.2% of all GI cancers and approximately 4% being SCC(8).

The median age of presentation of epithelial GBC in India is slightly younger as compared to western counterparts with an average age of 51±12 years (9). According to the published data median age of presentation for SCC is 65 years (range 43-83 years) (8). Here we reported 3 cases of ages 83, 53 and 47 respectively which is consistent with the published data.

SCC are very aggressive tumors with most of them presenting with metastatic disease de novo. Most common site for metastasis is liver (60%) followed by lungs (10%) (8). In our series one patient presented with de novo metastatic disease and other 2 presented with locally advanced non-metastatic disease.

On pathological examination SCC is commonly seen as diffuse thickening or nodular masses. Microscopically they are poorly differentiated carcinomas with high nuclear: cytoplasmic ration with a high mitotic rate. They are predominantly small blue round cell tumors and on IHC they are positive for synaptophysin, chromogranin or neuron specific enolase (NSE) (10). In our series all the patient had poorly differentiated small cell pattern and were positive for either synaptophysin, chromogranin or NSE on IHC.

The World Health Organization (WHO) has classified NEN into three grades depending on the mitosis or mitotic index (Ki-67) (11). Neuroendocrine carcinomas either large cell or small cell are defined as having mitotic rate >20 per mm^2 or Ki-67 >20%. Recently, WHO has used molecular classification for differentiation of NEN. In our series molecular analysis was not done due to non-availability of the test, however all the cases had Ki-67 >20% hence were reported as small cell carcinoma.

CECT scan or Positron Emission Tomography (PET CT) is important for staging and work up of SCC cases which will help in deciding further treatment. Depending upon the extent and general condition of patient surgery also plays an important role with either cholecystectomy alone or radical cholecystectomy with lymph node dissection or adjacent liver resection may be done. Mostly, patients present with advanced stage, due to systemic nature of the disease and upfront inoperability multiagent chemotherapy plays a significant role in the management of such cases. Various chemotherapy agents used are cisplatin, etoposide, gemcitabine and 5-FU (12). Pandey L et *al.* reported a series of 3 cases of SCC GB all of them received chemotherapy with etoposide and platinum with one patient received chemotherapy after surgery as adjuvant and rest upfront (13). In our series similarly one patient underwent upfront surgery followed by chemotherapy with etoposide and cisplatin and rest of the two patients received upfront therapy.

Outcome of SCC GB is very poor with a median survival of 4-5 months with 5 year survival of less than 5% (6). Our series also reported a poor survival with one patient surviving 7 months, one for 13 months and one is still alive post 2 months after treatment.

CONCLUSION:

SCC of GB is a rare malignancy with aggressive clinical course. Due to paucity of available literature and no formal randomized trials treatment is mostly based on published data and the clinical condition of patient. Multiagent chemotherapy plays an important role in management of the cancers. It represents as a clinical challenge in daily practice due to paucity of data and its rare occurrence.

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