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Primary Neuroendocrine Carcinoma of Gallbladder Revisited: An Evaluation and Reassessment of Management Strategy

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KEYWORDS

Neuroendocrine tumor, Gall bladder, Ki-67, Grade, Chromogranin, metastasis.

ABSTRACT:

Background: Primary neuroendocrine carcinoma of the gall bladder (GB) is an unusual entity. It accounts for 0.2% of all neuroendocrine tumors. It is usually characterized by late diagnosis and poor prognosis.

Materials and Methods: On retrospective analysis of patient record of GBC patients treated in our institute, we identified seven cases of primary gall bladder neuroendocrine tumor over last 5 years (August 2010 to October 2014). It represents 2.6% of all primary gall bladder carcinoma patients (630 patients). Data regarding clinical features, radiological findings, treatment aspects and their disease outcome was recorded and analyzed.

Results: All seven patients were female (mean age of 46.8 years) presented with locally advanced (n=4) and metastatic disease (n=3)[one in stage IIIA, two in stage III B, one patient in stage IIIA and three patients in stage IVB]. Pain abdomen was the most common presenting symptom. Three patients underwent definitive surgery, while four patients with palliative chemotherapy in view of distant disease/ locally advanced disease (inoperable). Final diagnosis of NEC was made on histopathological and immunohistochemical examination (IHC) of the resection specimen (N=3) or image guided biopsy tissue (N=4). Immunohistochemistry (IHC) studies revealed positivity of tumor cells for chromogranin (100%), synaptophysin (85.7%), NSE (85.7%) and Cytokeratin in all patients (100%). Five patients were in WHO grade 3 (poorly differentiated) and two in intermediate grade (moderately differentiated). Patients had a mean follow up of 11months (range: 8- 20 months). A correlation was seen with the poor differentiation of the tumor and high Ki-67 proliferative index with poor patient survival. Patients treated with definitive surgery had a mean survival duration of 12.6 months (range: 8 - 14 months), with local recurrence in one patient. Patients with metastasis treated with palliative chemotherapy had a mean disease control rate of 9.1 months (range 8 -12 months).

Conclusion: We present this case series to highlight the rarity of this entity, discuss the disease outcome and utility of immunohistochemical analysis in its identification. Ki-67 index and poor differentiation may be a predictive/prognostic marker of progressive disease. Surgery is the mainstay of treatment with ill-defined role of chemo radiotherapy with poor disease outcome.

INTRODUCTION

Gall bladder carcinoma (GBC) is the fifth most common gastrointestinal cancer with around 7000 new cases of gall bladder carcinoma diagnosed annually worldwide [1]. GBC is characterized by its insidious onset, paucity of early signs and symptoms and advanced stage of presentation, making its early diagnosis and subsequent curative treatment difficult [2]. North Indian Gangetic planes report one of the highest incidences of GBC in the world. Most common histological subtype of GBC is adenocarcinoma (80-95%). Less commonly described histological subtypes of GBC are

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undifferentiated/anaplastic carcinoma (2-7%), squamous cell carcinoma (1-6%), adenosquamous (1-4%) and carcinosarcoma (<1%), while neuroendocrine carcinoma is a rarely described subtype [3]. Primary neuroendocrine carcinoma of the gall bladder (GB NEC) is very infrequently described and is usually an incidental diagnosis during post-operative histological examination.

The first case of GB NEC was described by Joel in 1929 [4]. Tumors with neuroendocrine differentiation are classified by WHO as well differentiated (Malignant carcinoids), small cell endocrine carcinomas (poorly differentiated endocrine carcinoma) and mixed endocrine-exocrine carcinomas [5]. Majority of GB NEC reported in the literature are usually non secretory in nature [5]. Non secretory NECs often present with symptoms due to local disease progression and distant metastasis in contrast to secretory carcinoid tumors which usually present with symptoms related to secretory peptides. Classical Carcinoids are rarely metastatic or invasive in nature, whereas atypical NECs are highly aggressive and carry a poor prognosis [5].

We report a series of seven cases of GB NECs (non secretory type) and discuss their clinic-pathological presentation, treatment and disease outcome.

METHODS

In this retro prospective study, to analyze the clinical course and treatment outcome of GB NEC histological subtype, all cases with histological diagnosis of gall bladder carcinoma treated at our institution were identified and analyzed (August 2010 to October 2014). Their histopathology was reviewed and non-adenocarcinoma cases with a suspicion of endocrine differentiation based on small cells with rounded nuclei and granular chromatin were identified and subjected to immunohistochemistry studies (IHC). We were able to identify seven cases of gall bladder neuroendocrine carcinoma at our institution between August 2010 to October 2014. The immunohistochemical markers used for identification of GB NEC were pancytokeratin [Pan CK] (for substantiating the diagnosis of carcinoma), synatophysin, chromogranin [CG] and neuron specific enolase [NSE] (for determining endocrine nature of tumor cells) and Ki-67 (for determining the proliferative capacity of the tumor cells). Out of 630 cases of GBC identified over 5 year study period, only 7 cases of NEC were identified retrospectively based on IHC studies. The demographic profile, radiological features, final histopathology and immunohistochemical analysis, treatment modalities and outcome were recorded and analyzed. Amongst these seven patients, three underwent definitive surgery with postoperative histological diagnosis of NEC, while four patients with locally advanced / metastatic disease were diagnosed on image guided biopsy.

RESULTS

Seven cases of gall bladder neuroendocrine carcinoma [GB NECs] were identified, representing 0.9% of all primary gall bladder carcinoma (N=630) treated in our institution during the study period (August 2010 to October 2014). All patients were female with a mean age of 51.5 years [range = 30-65]. All patients were relatively well preserved with Eastern Cooperative Oncology Group [ECOG] 0/1 status at presentation. Presenting symptoms in majority of patients were gradually worsening upper pain abdomen (n=7), lump in right upper quadrant of abdomen (n=5) and weight loss\loss of appetite (n=4). No history of previous cholecystectomy was noted in any patient.

Physical examination revealed palpable lump in right hypochondrium in five patients, ascitis in one patient and palpable supraclavicular node in one patient. In all patients, serum alkaline phosphatase was mildly elevated [mean 345 IU/ml (range= 142-822)] and serum bilirubin level was normal in all patients. All patients underwent contrast enhanced computed tomography (CECT) scan of the abdomen and chest X-ray as a part of routine staging workup. Five out of seven patients (68.9%) had co-existent cholelithiasis. CT scan showed GB mass in all patients with adjacent liver involvement in four patients; non contiguous liver lesions with peripheral enhancement in three patients and loco-regional lymphadenopathy in five patients [table no 1].

Table 1: Clinicopathological features of the GB NEC patients.

Parameters	
Age (years)	
≤ 30	1
31 - 50	2
51 - 70	4
> 70	0
Mean age	51.5[range=30-65]
Sex	
Female	7
Male	0
ECOG status	
0	03

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1	04
2	00
Cholelithiasis	
Yes	4
No	3
Symptoms	
Abdominal pain	7
Lump abdomen	5
Jaundice	0
Loss of appetite/ weight loss	4
Signs	
Lump upper abdomen	5
Jaundice	0
Ascitis	1
Supraclavicular lymphnode	1
Liver function test	
Serum bilirubin	0.8mg /dl [range=0.6-1.2]
Alkaline phosphatase	345IU/ml [range= 142-822]
Extent of disease	
Mass in gallbladder	7
fossa	4
Contiguous liver invasion	5
Locoregional adenopathy	3
Noncontiguous liver metastasis Ascitis	1
Metastasis	
Present	03
Absent	04
Stage	
IIIA	01
IIIB	02
IVA	01
IVB	03

Management: After radiological exclusion of major vascular involvement / non contiguous liver infiltration and paraaortic adenopathy and a preoperative diagnosis of GBC, three patients were planned for exploratory laparotomy and underwent radical cholecystectomy with segment 4b and 5 liver resection, and common bile duct preserving hepatoduodenal ligament lymph node clearance in order to achieve R0 resection. Postoperative course was uneventful with no major bile leak and histopathology revealed clear resection margin of gall bladder bed and liver. Lymph nodes were positive in two patients with mean node retrieval of six nodes [range: 4-8 nodes]. Two of the three patients undergoing surgical resection subsequently received adjuvant chemotherapy (Cisplatin & Etoposide) in view of nodal positivity. The remaining four patients showed radiologic evidence of metastasis on presentation and underwent computed tomography guided biopsy from gall bladder mass/liver metastasis. Histological examination of the biopsy revealed the diagnosis of NEC which was confirmed by IHC studies. All four patients with metastatic disease received palliative chemotherapy (Cisplatin & Etoposide) till disease progression.

Histopathology: Final diagnosis of NEC was made on histopathological examination and immunohistochemistry (IHC) of the resection specimen or guided biopsy tissue. Immunohistochemical (IHC) analysis revealed that tumor cells expressed cytoplasmic positivity for chromogranin [CG] in all seven patients (100%). Strong positivity for chromogranin [CG] was seen in five and focal positivity in two patients respectively. Tumor cells were positive for synaptophysin in six patients (85.7% cases), neuron specific enolase in six patients [NSE] (85.7%) and cytokeratin [CK] in all patients (100%).

Grading and differentiation: Proliferative rate was assessed based on mitotic count (number of mitosis per 10 high power field [HPF] of tumor tissue and Ki-67 proliferation index (the percentage of tumor cells staining positive for Ki-67 nuclear antibody). Histological grading of tumors based on WHO grading was done (Grade 1: well differentiated [greater than 95% of tumor composed of glands], Grade 2: moderately differentiated [50 - 95% of tumor composed of glands], Grade 3: poorly differentiated [5-49 % of tumor composed of glands] and grade 4 carcinomas (undifferentiated). In the present study, according to WHO grading, five patients were in grade 3 (poorly differentiated) and two in intermediate grade (moderately

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differentiated). NETs are generally divided into well and poorly differentiated categories.

An inverse correlation was seen with the poor differentiation of the tumor and high Ki-67 proliferative index with patient survival. Out of five patients with poor differentiation and Ki-67 more than 25%, three patients showed poor response to treatment, in the form of either early recurrence or disease progression. Ki-67 index and poor differentiation may be a prognostic marker of early disease progression especially in inoperable/metastatic GB NECs and may aid in identification of poor responders and thus needs to be studied further.

Follow up and outcome: Two of the three patients treated with definitive surgery had no evidence of recurrence of disease during follow up period of 15 months, while other patient with poor differentiation and Ki-67 more than 20% had local and distant recurrence after a disease free interval of 14 months. Amongst patients with metastatic disease, two patients showed stable disease [one patient belonged to well differentiation and Ki- 67 <10%] and two patients [poor differentiation and Ki-67 >20%] progressed on chemotherapy.

Patients had a mean follow up of 11months (range: 8- 20 months). Patients treated with definitive surgery had a mean survival rate of 12.6 months (range: 8 - 15 months), with local recurrence at liver bed in one patient with high Ki-67 and poor differentiation. Metastatic patients treated with palliative chemotherapy had a mean disease control rate [DCR] of 9.1 months (range 8 -12 months).

Table 2: IHC expression in the following seven gallbladder neuroendocrine carcinoma patients

Cases	Stage	CG	SP	NSE	CK -7	Ki-67	Mitotic rate/10HPF	Histological Grading	Differentiation
1	3B	+ve	+ve	+ve	+ve	40%	>25	3	Poor
2	4B	+ve (focal)	+ve	+ve	+ve (focal)	25%	20-25	3	Poor
3	3B	+ve	+ve	+ve	+ve (focal)	20%	14-15	2	Well
4	4B	+ve	-ve	+ve	+ve	30%	25-30	3	Poor
5	4A	+ve	+ve (focal)	-ve	+ve	10%	8-10	2	Well
6	4B	+ve	+ve	+ve (focal)	+ve	80%	40-45	3	Poor
7	3A	+ve (focal)	+ve	+ve	+ve (focal)	25%	20-25	3	Poor

CG- chromogranin, SP- synaptophysin, NSE- neuron specific enolase, CK- Cytokeratin. Ki-67/Mib 1 index-proliferative index.

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Table 3: Treatment modalities and outcome of 7 Gallbladder neuroendocrine tumor patients

Pall- palliative, CT- chemotherapy, * - Expired

Case	Stage at diagnosis	Treatment modality	Disease free survival (DFS) / Disease control rate (DCR)	Local recurrence \ progression
1	3B	Surgery+Adjuvant CT	14	Recurrence*
2	4B	Pall CT	8	Progression
3	3B	Surgery+ Adjuvant CT	12	Disease free
4	4B	Pall CT	12	Progression
5	4A	Pall CT	8	Stable disease
6	4B	Pall CT	9	Stable disease
7	3A	Surgery	8	Disease free

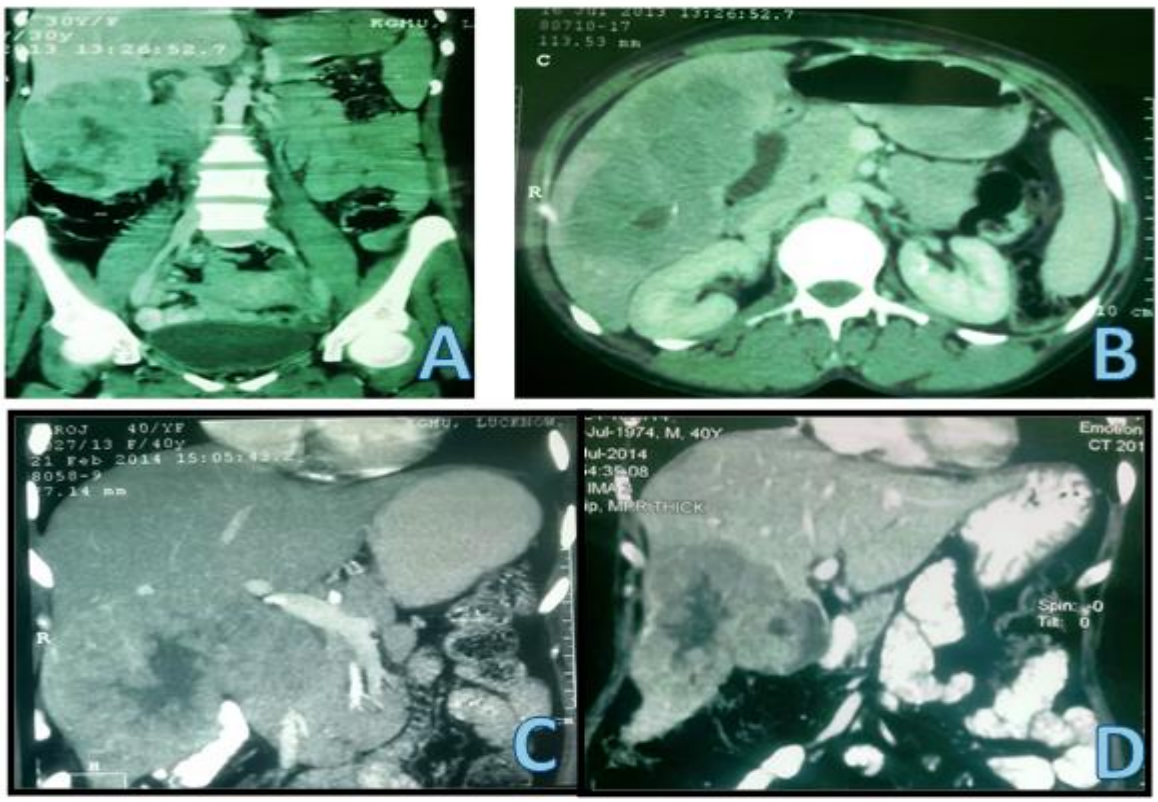

Figure 1 A & B. Exophytic heterogeneous mass arising from body of gall bladder with infiltration of liver.

Figure 1C. Pre-chemotherapy CT scan showing exophytic GB mass with extensive liver infiltration (Segment V,VI & VII).

Figure 1D. Post chemotherapy CT scan showing stable disease after 4 cycles of combination chemotherapy (Cisplatin & Etoposide).

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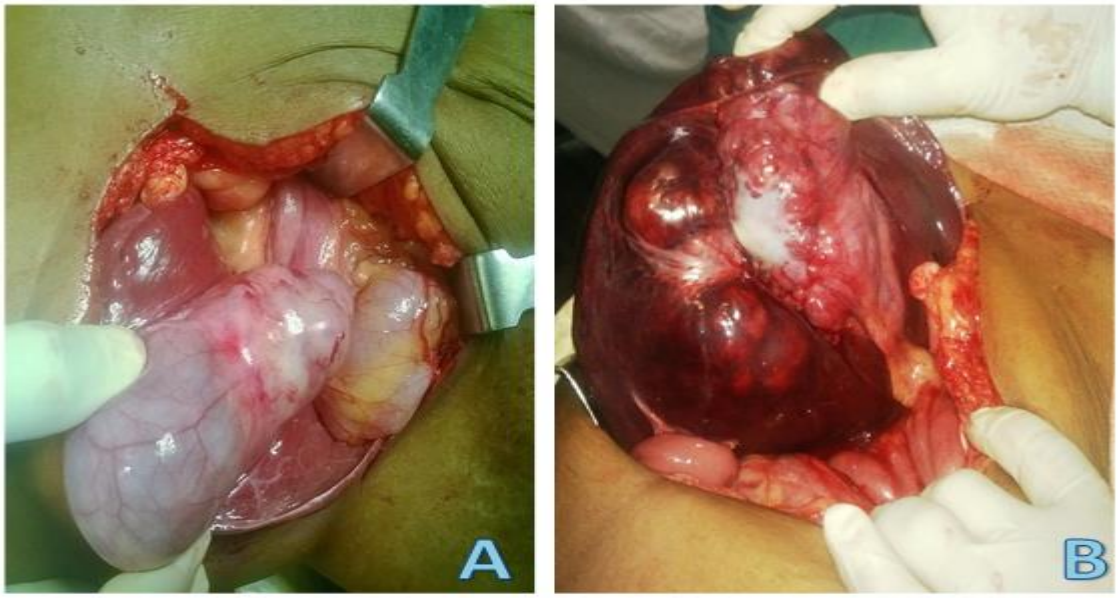

Figure 2A: Tumor arising from body of gallbladder with minimal adjoining liver infiltration.

Figure 2B Tumor arising from fundus and body of gall bladder with scarring and fibrosis and adjoining hepatic infiltration (Segment IVB , V) .

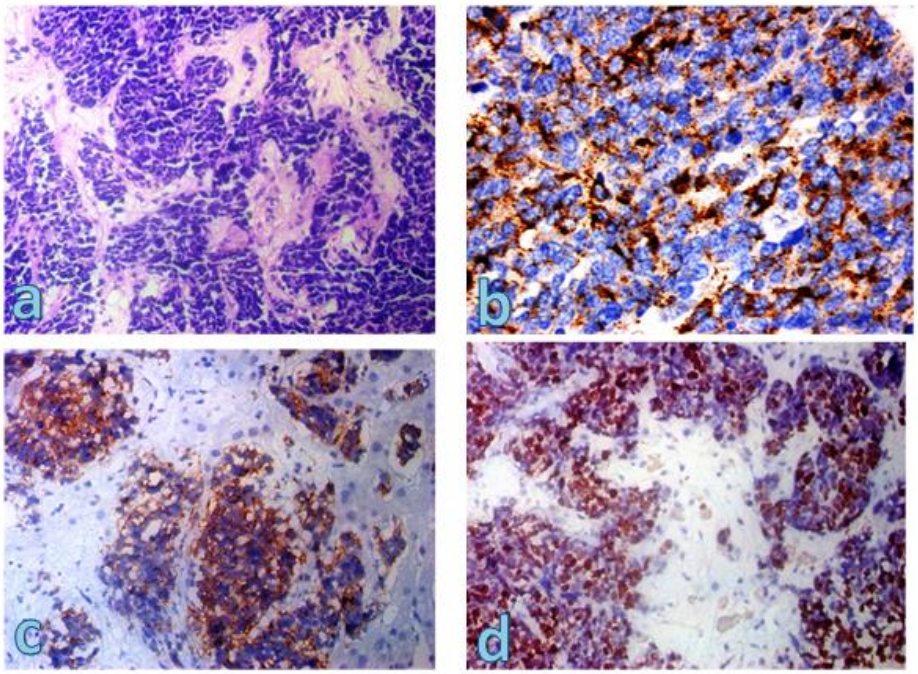

Figure 3A: Photomicrograph shows nests of monomorphic small round tumor cells with hyperchromatic nuclei and scant cytoplasm. (Hematoxylin & Eosin, x200).

Figure 3B: Section shows nests of tumor cells with cytoplasmic positivity for Chromogranin.

Figure 3C: Section shows nests of tumor cells with granular cytoplasmic positivity for Synaptophysin.

Figure 3 D: Section shows nuclear positivity for Ki-67 in about 40 % of tumor nuclei. (Di-aminobenzidine, x200).

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DISCUSSION

Gall bladder cancer is the most common type of biliary tract cancer and sixth most common type of digestive tract malignancy [1]. GBC is presumed to be the most aggressive of the biliary tract cancers with the shortest median survival. North Indian Gangetic planes report one of the highest incidences of GBC in the world. It is the one of the commonest gastrointestinal cancer affecting north Indian females. Neuroendocrine tumors/ Carcinoids are relatively rare endocrine tumors and comprise less than 2% of all primary gastrointestinal tumors. Most common sites for primary carcinoid tumor are appendix, jejunum and rectum. Unusual sites include duodenum, colon and stomach. Gall bladder is an exceptionally infrequent site for primary neuroendocrine/ carcinoid tumor. According to Sanders, there were only seven cases of GB NETs described among 3633 digestive tract NETs accounting for only 0.2%[7] whereas only one case of gall bladder NETs was reported from among 2837 digestive NETs (0.04%), as per a study by Godwin [8].

Though exact aetiopathogenesis is not clearly elucidated, majority of GB NETs are thought to arise from preexisting endocrine cells in the neck of gall bladder. Recent evidence point to their origin from multipotent stem cells or neuroendocrine cells in intestinal or gastric metaplasia of the gallbladder epithelium, secondary to long standing inflammation from cholelithiasis [9, 10]. Role of genetic factors in the oncogenesis and progression of these tumors is not well established [11]. Based on an extensive literature review, the age of the patients with GB NETs ranged from 38-81 years with a marked female predominance. In the present study, the age of the patients ranged from 30 to 65 (mean age-51.5 years) and all patients were female, in consonance with the literature [12].

The clinical and radiological presentation of GB NETs seems to be identical to that of gall bladder carcinoma. Majority of cases of NETs are initially asymptomatic, as most tumors are non secretory in nature in contrast to other gastrointestinal NETs. Most common presenting symptom is often vague and gradually progressive abdominal pain/ discomfort, usually with a palpable lump in right hypochondrium. In the present study, all patients presented with nonspecific pain abdomen, while palpable lump at presentation was present in five patients. None of the patients had any symptoms suggestive of secretory peptides being produced by tumor [non secretory]. Approximately 3.3 to 3.7% of gastrointestinal/GB NETs present with carcinoid syndrome secondary to secretory peptides [13]. Radiologic features are usually non specific and mimic gall bladder carcinoma therefore specific preoperative diagnosis of GB NETs is extremely difficult based on radiological features alone [14,15]. In the present case series, imaging showed large gall bladder mass with adjacent liver infiltration in 3 patients and non contiguous liver metastatic deposits in 3 patients. In the present study, around 42.8 % neuroendocrine tumors were localized (operable), one patient had locally advanced disease and 42.8% patients were found with non contiguous liver metastasis. Majority of NET of gall bladder are diagnosed on routine post-operative histopathological examination of gall bladder specimen.

Based on the grade of tumor, NETs are classified into well differentiated and poorly differentiated sub groups. The term “well differentiated NETs” refers to low and intermediate grade tumors, while poorly differentiated tumors include high grade tumors [16,17]. Grading of the tumor is based on the number of mitotic figure per 10 high power fields and percentage of tumors cells which stain positive for the proliferative marker Ki-67. Low grade tumors have an indolent course, intermediate grade NETs are moderately aggressive with a less predictable course and high grade NETs are usually aggressive in nature and have a dismal prognosis [18-21]. In the present study, five patients had high grade NETs and two patients had intermediate grade tumor. Based on Ki-67 and mitotic rate, five NETs belonged to poorly differentiated category, whereas two NET were well differentiated in nature.

Mizukami *et al.* and Kaiho *et al.* described the hallmark pathological features that differentiate the classical carcinoid tumors from their carcinomatous counterparts. Histologically, tumor consists of diffuse sheets, nests and focal acinar patterns, small to large sized round cells having high nucleo-cytoplasmic ratio, pleomorphic nuclei with speckled chromatin and scanty cytoplasm. Atypical carcinoids have marked cellular atypia and mitosis as compared to classical carcinoid[22]. Small cell nature of the lesion mandates immunohistochemistry for further characterization of the tumor. Based on immunohistochemistry analysis, Soga *et al.* reported that 100% of well differentiated NETs stain positive for Chromogranin and Neuron specific enolase [NSE] (93.8%) commonly [23]. In the present study, Immunohistochemistry (IHC) studies revealed that the tumor cells were positive for Chromogranin in all seven patients (100%), Synaptophysin and NSE in 85.7% and Cytokeratin in all patients (100%). According to WHO grading, five patients were in grade 3 (poorly differentiated) and two in intermediate grade (moderately differentiated) [17].

Prognostic factors determining the outcome of GB NETs include tumor size, grade, differentiation and regional / distant metastasis. An inverse correlation was seen with

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the poor differentiation of the tumor, high Ki-67 proliferative index and patient survival with three out of five patients with poor differentiation, high Ki-67 index showed early disease recurrence or poor response to palliative chemotherapy. Similar findings were reported by Eltawil *et al.* who concluded in their study that elevated Ki-67 and high mitotic index may be predictive of poor outcome in GB NETs as has been described in other NETs [24]. This is in contrast to study by Iype *et al.* which concluded that chemotherapy was more effective for small-cell subtype of GB NECs [25].

Biological targeted therapies (like somatostatin analogs) have traditionally been used for controllong symptoms in patients with gastrointestinal NETs [26]. Although PET with Fludeoxyglucose (18F) is an established technique for functional oncological imaging, it has not proven as successful for imaging NETs, except for highly aggressive tumors [14]. Based on the ability of NETs to take up decarboxylate amine precursors, 11-C labeled and 18-F labeled amine precursors such as 5-HTP and L-DOPA PET may hold promise for visualizing NETs [27].

Definitive surgical resection wherever possible offers best chance of long term cure but unfortunately, resection is possible in only 25% of patients due to advanced nature of their disease at presentation. Surgical treatment includes simple/radical cholecystectomy with hepatoduodenal ligament clearance with or without adjacent local organ resection with aim to achieve margin negative resection [24]. Multimodality treatment approach for GB NETs consisting of surgery, chemotherapy and receptor radionuclide therapy is still not clearly defined. Adjuvant chemotherapy (Cisplatin/Carboplatin & Etoposide most commonly employed regimen) may be given in patients with node positivity, liver or adjacent organ involvement.

Various anecdotal reports describe use of several chemotherapeutic agents including Cisplatin, Doxorubicin, Gemcitabine, 5-fluorouracil, Etoposide with variable response rates. Role of radiotherapy is debatable [28]. No well defined protocols for adjuvant chemotherapy or chemotherapy in palliative settings for GNB NETs are on record. Improved outcomes have been observed with aggressive radical surgery in GBC and some reports have shown that patients with a local invasive NEC of the gall bladder may benefit from aggressive surgical treatment, followed by adjuvant chemotherapy [29]. In patients with unresectable tumors, systemic therapy is the treatment of choice [30].

In the present study, three patients underwent radical cholecystectomy. Two patients received adjuvant chemotherapy [cispaltin and etoposide (C+E regimen x 6 cycles) in view of nodal positivity. All four patients [3 with metastatic disease and 1 with locally advanced] received palliative chemotherapy [Cisplatin and Etoposide (C+E regimen) till disease progression. Two patients showed stable disease for 8 months and two progressed on chemotherapy after 6-8 cycles. Randomized, blinded trials for better treatment protocols in the management of GB NETs or to validate one regimen as the standard treatment are highly recommended but rarity of GB NETs makes this an uphill task.

In this study, patients had a mean follow up of 12 months (range: 8- 20 months). Patients treated with definitive surgery had a mean survival duration of 12.6 months (range: 8 - 14 months), with local recurrence in GB fossa in one patient. Patients with metastasis who were treated with palliative chemotherapy had mean disease control duration of 9.1 months (range 8 -12 months).

In conclusion, primary neuroendocrine tumor of the gall bladder is an uncommon entity with dismal prognosis. Exact etiology is not clearly elucidated. Due to non-specific clinical features and radiological findings, it is difficult to differentiate GB NETs from gall bladder carcinoma. Most GB NEC is incidentally diagnosed based on post-operative histopathological examination and immunohistochemistry. Surgical resection is the mainstay of management with poorly defined role of adjuvant chemo-radiotherapy. Chemotherapy may have a role in inoperable and metastatic setting. There is a need to stratify GB NETs into different histological grades based on Ki-67 proliferation index and mitotic rate, which may also be used for tumor prognostication as each grade may have a different metastatic potential, prognosis and clinical course. We present this series of seven NETs to highlight their rarity and discuss the prognostic factors which define the tumor biology of this rare entity. Though a rare entity, primary GB NEC should be considered in the differential diagnosis of gallbladder carcinoma.

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