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Reviewer Article

Primary neuroendocrine tumors of the gall bladder: Morphology with corroborative immunohistochemistry is the key to diagnosis

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ABSTRACT

Neoplasms with neuroendocrine differentiation comprising both neuroendocrine tumors (NETs) and neuroendocrine carcinomas (NECs) arising in gall bladder are extremely rare. NETs of the gall bladder represent only 0.2% of all NETs, whereas NECs comprise of 4% cases of all the malignant neoplasms of the gall bladder. NEC is the most aggressive variant of all gall bladder carcinomas. In most of the cases diagnosis is incidental and patient usually presents at advanced stage as there are no specific clinical or radiological features to detect NECs pre-operatively. Histopathology of the resected specimen and immunochemical analysis remain the main stay of diagnosing these malignancies. This case report includes 3 cases of NECs gall bladder comprising of two cases of small cell NECs and one case of large cell NEC. Although surgery followed by chemotherapy play important role in improving the quality of life of the patients, the prognosis of this combative disease can be upgraded by understanding the biological behavior of these tumours to adapt a definitive treatment protocol. The main aim of this study is to highlight on the need for better assessment, detection and management of this rare and aggressive entity to improve the survival rate of the patients of NECs.

1. Introduction

Gall bladder carcinoma which was first described by deStoll in 1777 is one of the rare disease worldwide, however it is the sixth most common and extremely lethal malignancy of the biliary tract with shortest survival rate from the time of diagnosis.[1] Gall bladder malignancies have a peculiar geographic variation with higher incidence in Asian countries. Worldwide the highest incidence rate has been reported in females of Delhi, India (21.5/100000 population per year). The exact reason for higher incidence among this population has not been understood yet but it is hypothesized that increasing gall stones may be the causative factor.[2] The etiology is multifactorial with the most common risk factor being gall stones (4-7 times more risk than general population), other risk factors include gall bladder polyp usually of size $>$ 1 cm, porcelain gall bladder, adenomyomatosis of gall bladder, xanthogranulomatous cholecystitis, salmonella typhii infection, dietary, environmental and genetic factors.[3,4] In gall bladder the most common malignancy is adenocarcinoma (90-95%), and the primary neuroendocrine carcinomas are exceedingly rare in the gallbladder. The first case of primary neuroendocrine tumor was reported by Joel in 1929.[5] Since then few other cases of neuroendocrine neoplasms have been reported. Neuroendocrine neoplasms emerge from the neuroendocrine cells which constitute the largest group of hormone producing cells in the body. The most common location of neuroendocrine tumors (NETs) is gastrointestinal tract (66%) followed by lungs (31%). Less frequently they may occur in other locations like ovaries, testes, hepatobiliary system and pancreas. Gall bladder lacks neuroendocrine cells, therefore the primary neuroendocrine neoplasms of the gall bladder theoretically arise from a pleuripotent stem cell

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or from the metaplasia in the gall bladder due to result of chronic inflammation.[1] According to the current WHO classification neuroendocrine neoplasms are classified into four broad categories, NETs (Grade 1 and 2) which were previously known as typical carcinoids, neuroendocrine carcinomas (large cell and small cell) and mixed adenoneuroendocrine carcinoma(MANEC). According to the Surveillance Epidemiology and End Results (SEER) program the incidence of the neuroendocrine neoplasms has increased, however due to paucity of the cases there are only few studies available to understand the biological behavior, mechanism, pathogenesis and treatment protocol of these tumors. The NETs of gall bladder represent only 0.2% of all NETs, whereas NECs comprise 4% cases of all malignant neoplasms of the gall bladder. Neuroendocrine neoplasms can occur in any portion of the gall bladder including fundus, body or neck. The average age of presentation is 65 years with mean range of 43-83 years. They are more common in females with male to female ratio of 1:1.8.[6] In females the risk increases with higher gravidity and parity. There are no specific symptoms or pathognomonic radiological modalities to diagnose gall bladder neuroendocrine cancer pre-operatively. Most of the GB neuroendocrine tumors are incidentally diagnosed after routine cholecystectomy for cholecystitis or after surgery for suspected biliary pathology. We report three cases of gall bladder neuroendocrine tumors, two cases were reported as small cell NEC and one as large cell NEC. All the three patients underwent radical surgery and were referred for chemotherapy. The presentation of our cases is justified by the rarity of the tumor, non-specific symptoms and radiological imaging findings as well as paucity of the literature, uncertain prognosis and no certain treatment modalities. This also highlights the importance of mandatory histopathological evaluations of all the cholecystectomy specimens.

2. Case Reports

2.1. Case 1

51 years old male with no comorbidities presented with complaint of colicky pain of moderate to severe intensity in right upper abdomen associated with nausea and vomiting since 1 month. The pain was constant and non-radiating which was relieved with analgesics. The laboratory results including complete blood count and biochemistry were normal. On per abdominal examination tenderness was present. Ultrasound examination revealed cholelithiasis with sludge ball/soft tissue mass and prominent CBD. Contrast enhanced CT demonstrated enhancing irregular concentric mural wall thickening of GB wall with large enhancing intraluminal soft tissue component infiltration into the adjacent hepatic parenchyma, forming a large lobulated necrotic mass lesion, measuring approximately 59 x 74 x 75mm. (Figure 1a) Triple phase CT abdomen was also done in this case showed heterogeneously enhancing mass in the GB fossa invading into segment 4 and 5 of liver, pylorus, first part of duodenum, mesentery, hepatic flexure of colon and parietal abdominal wall with portal vein and CBD involvement and enlarged lymph nodes. On the basis of clinical and radiological assessment diagnosis of gall bladder carcinoma was made.

A conglomerated specimen comprising of gall bladder, liver, duodenum, colon and pancreas measuring 24 x 14.5 x 11 cm was sent for histopathological examination. Gall bladder measured 9 x 5 cm and cut surface showed an ulcero-infiltrative grey white mass measuring 8.5 x 7.5 x 5 cm involving neck, body and fundus of the gall bladder. (Figure 1b) The tumour involved liver, colon and duodenum grossly. Multiple yellowish stones were also noted impacted within the gall bladder mass.

Histopathological examination showed an invasive tumour arranged in sheets, trabeculae, tubules as well as in solid nests separated by fibrovascular septae. The tumor cells were medium to large sized with central round to oval uniform nuclei, prominent nucleoli, finely stippled chromatin and variable amount of eosinophilic cytoplasm. Few rosette like structures were identified. Many multinucleated tumor giant cells and bizzare cells were seen. The stroma was richly vascularized and showed nodular infiltrates of foamy macrophages, many multinucleated foreign body type of giant cells, pigment laden macrophages, lymphocytes, plasma cells, neutrophils, eosinophils, histiocytes and proliferating blood vessels as well as lymphoid aggregates along with areas of fibrosis. (Figure 2a, Figure 2b) Large areas of necrosis and haemorrhage were present. Adjacent mucosa of the gall bladder showed focal pyloric metaplasia. (Figure 2d) Mitotic activity markedly increased (approximately 30 -35 mitoses/10HPF) with many atypical mitotic figuresnoted. Foci of lymphovascular as well as perineural invasion identified. The tumour was seen invading into the adjacent liver bed, duodenum and colon. (Figure 2c) In this case 29 lymph nodes were dissected out and 06 of them showed metastatic tumor deposits. On immunohistochemistry the tumour cells showed positive staining for synaptophysin, chromogranin and negative staining for cytokeratin. (Figure 2e, Figure 2f) The ki67 index was high (75-80%). On the basis of immunohistochemistry and histopathological findings the final diagnosis was Large neuroendocrine carcinoma (G3-Poorly differentiated, TNM staging: pT3pN2M0).

2.2. Case 2

43 years female presented with the history of on and off diffuse abdominal pain since 1 year. There was no other associated complaint and the past history was non-contributory. The review of all the systems was

grossly unremarkable. CT scan performed revealed a polypoidal growth suggestive of ill-defined mass in the gall bladder measuring 43.6x 32 mm with loss of fat planes. (Figure 3a) The basic laboratory investigations were within normal limits. Clinically the patient was diagnosed as gall bladder carcinoma and taken up for radical cholecystectomy. Following surgery the specimen was sent for histopathological analysis. We received partially cut open specimen of gall bladder with liver wedge altogether measuring 10 x 8 x 5 cm. Cut surface showed a greyish to yellowish white polypoidal mass involving the body and fundus of the gall bladder measuring 5 x 4 x 2.75. (Figure 3b) Grossly the mass was well confined within the lumen of the gall bladder and not involving the liver.

2.3. Case 3

36 years old female patient presented with short history of pain abdomen in the right upper quadrant associated with jaundice and fever since 3 months. MRCP was suggestive of cholelithiasis with cystic duct and CHD calculus causing dilatation and bilateral IHBR. Patient denied of any significant past surgical and family history. Clinically the case was diagnosed as gall stone disease,laproscopic cholecystectomy was performed and specimen sent for histopathological examination. On gross examination the gall bladder measured 12 x 5 cm with presence of single calculi lying separately within the container. However, cut surface of the specimen showed a polypoidal greyish white growth measuring 3 x 2.2 x 1.5 cm in the neck of the gall bladder.

Histopathological examination of both the cases 2 and 3 showed similar findings. The histology demonstrated round to oval cells arranged in sheets, nests, festoons and cords. The tumor cells had round to ovoid hyperchromatic nuclei, inconspicuous nucleoli, finely stippled chromatin and moderate to abundant eosinophilic cytoplasm. (Figure 4a, Figure 4b) Many cells showed nuclear moulding along with few rosette like structures also identified. The stroma was richly vascularized and showed nodular infiltrates of foamy macrophages, many multinucleated giant cells, pigment laden macrophages, lymphocytes, plasma cells, neutrophils, eosinophils, histiocytes and proliferating blood vessels as well as lymphoid aggregates along with areas of fibrosis. Large areas of necrosis and haemorrhage seen. Gall bladder epithelium showed intestinal metaplasia. (Figure 4c) Mitotic activity was markedly increased with presence ofmany atypical mitotic figures.

In the 2^{nd} case lymphovascular invasion was present, however perineural invasion was not identified. 08 out of 23 lymph nodes showed metastatic tumour deposits. In the 3^{rd} case cystic duct margin was positive and both lymphovascular as well as perineural invasion were noted. 01 out of 17 lymph nodes showed metastatic tumor deposits. On immunohistochemistry the tumor cells showed diffuse positivity for synaptophysin, scattered positivity for chromogranin and negative staining for cytokeratin.(Figure 4d, Figure 4e) The ki67 index was high (75-80%).(Figure 4f)The final diagnosis was Small cell neuroendocrine carcinoma (G3- Poorly differentiated). TNM staging of case 2 was pT2bpN2M0 and that of case 3 was pT2bpN1M0

Following surgery all the patients were referred for chemotherapy and are on regular follow up with no significant complications reported till date.

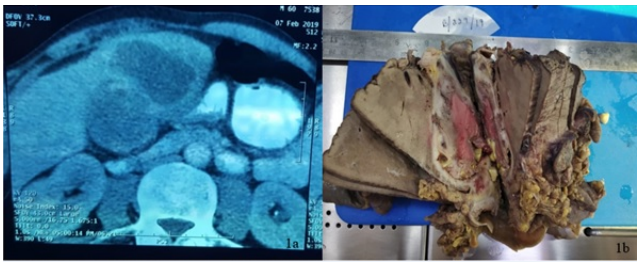

Fig. 1: a: CECT demonstrating enhancing mass in the gall bladder. **1b:** Gross specimen showing multiple stones and ulcero -infiltrative growth involving neck, body and fundus of the gall bladder infiltrating into the liverand duodenum grossly.

3. Discussion

Primary neuroendocrine carcinomas of the gall bladder are rare. The neuroendocrine tumors are the group of tumors which arise from neuroendocrine cells in the body and have predominantly neuroendocrine differentiation. The classification of neuroendocrine neoplasms is based on the tumor size, differentiation, morphological features, angioinvasion, mitotic activity and Ki67 index.[17]

According to current WHO classification neuroendocrine neoplasms are sub divided and graded based on the Ki67 labelling index and mitotic activity.[6] (Table 1)

1. Neuroendocrine tumors (N ET)
   a. NET grade 1 (carcinoids)
   b. NET grade 2
2. N euroendocr ine carcinoma (NEC)
   a. L arge cell NEC
   b. S mall cell NEC
3. Mixed adenoneu roendocrine carcinomas (MANEC)
4. Goblet cell carcinoids
5. Tubular carcinoids

Mixed neuroendocrine carcinomas (MANEC) comprises of both adenocarcinoma and NEC simultaneously with percentage of each component exceeding 30%.[6,16]

The origin of NETs was controversial because initially there was a concept that neuroendocrine cells arise from the neural crest cells and the normal gall bladder mucosa lacks neuroendocrine cells. But present they are validated to arise from the local multipotent gastrointestinal stem cells.

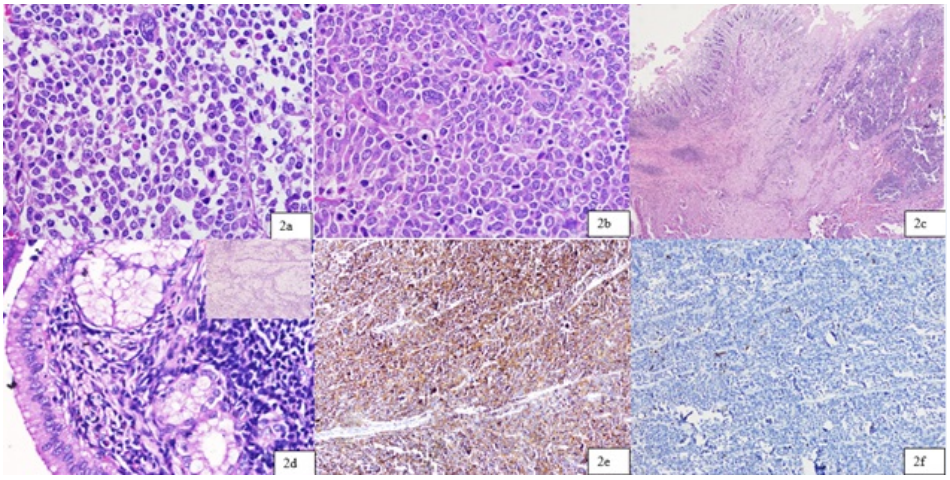

Fig. 2: 2a&2b (10x& 40x): Medium to large sized cells with central round to oval uniform nuclei, prominent nucleoli, finely stippled chromatin and variable amount of eosinophilic cytoplasm. Multinucleated tumor giant cells present. 2c(4x): Tumor cells invading duodenum. 2d (40x): Gall bladder epithelium showing pyloric metaplasia. Inset showing nodular infiltrates of foamy macrophages. 2e(10x): Diffuse synaptophysin positivity in the tumor cells. 2f(10x): Negative expression for cytokeratin in the tumor cells.

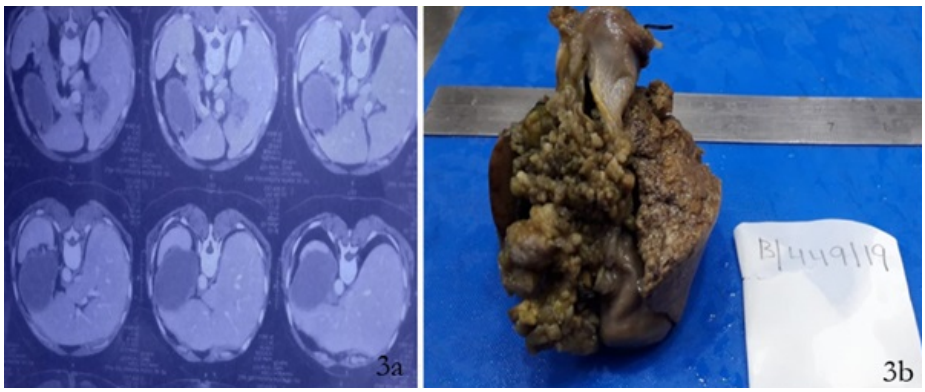

Fig. 3: 3a: CECT showing apolypoidal growth suggestive ofill-defined mass in the body of the gall bladder. 3b: Gross specimen with a polypoidal mass involving the body andfundus of the gall bladder

Table 1: WHO classification neuroendocrine neoplasms [6]

Differentiation	**Grade**	**Mitotic activity**	**Ki67 labelling index**	**Synonyms**	**WHO**
Well differentiated	Grade 1 (Low grade)	<2 mitoses/10HPF	<3%	Carcinoids, well differentiated endocrine tumour/carcinoma	Neuroendocrine tumour, G1
	Grade 2 (intermediate grade)	2-20 mitoses/10HPF	<3-20%		Neuroendocrine tumour, G2
Poorly differentiated	Grade 3(High grade)	>20 mitoses/10HPF	>20%	Poorly differentiated endocrine carcinomas, high grade neuroendocrine carcinomas, small cell and large cell endocrine carcinomas	Neuroendocrine carcinoma, G3, small cell Neuroendocrine carcinoma, G3, large cell

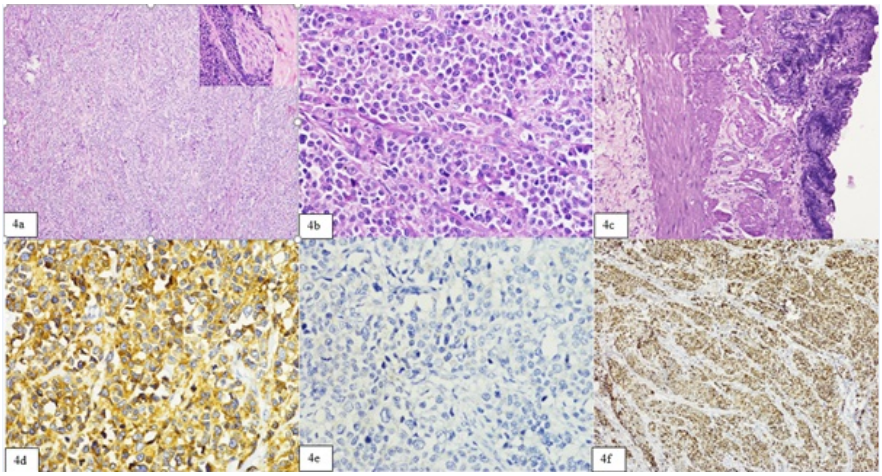

Fig. 4: 4a&4b(10x&40x): The tumor cells with round to ovoid hyperchromatic nuclei,inconspicuous nucleoli, finely stippled chromatin and moderate to abundanteosinophilic cytoplasm. Inset shows perineural invasion. 4c(10x): Gall bladderepithelium showing intestinal metaplasia. 4d(10x): Tumor cells showing diffusepositivity for chromogranin. 4e(10x): Negative staining for cytokeratin in thetumor cells. 4f(10x): High ki67 index (75-80%).

Table 2: Histologicaland management variation between small cell NEC and large cell NEC

S. No	Findings	Small cell NEC	Large cell NEC
1	Nucleus	Less than the size of three small resting lymphocytes.	More than 3 fold the diameter of small lymphocyte
2	Azzopardi phenomenon	Present	Usually absent
3	Nucleoli	Absent or Inconspicuous	Prominent
4	Nuclear moulding	Characteristic	May or may not be present
5	Rosette formation	Occasionally present	Often present
6	Chemotherapy	Good response	Poor response

Table 3: Comparisonof clinical spectrum, radiologicalfeatures and management of Small cell NEC in various studies with the presentstudy

Author	Age	Sex	Clinical presentation	Tumour location	Tumour size	Metastasis	Calculi	Surgical treatment
Mondal et al 2015 [7]	42	M	Right upper quadrant pain, weight loss	Neck	1.5 cm	Absent	Not mentioned	Cholecystectomy
Adachi et al 2016 [8]	79	F	Right upper quadrant abdominal pain	Not mentioned	3 cm	Liver	Present	Radical cholecystectomy with partial liver resection
Kumar et al 2018 [9(13)]	61	F	Pain abdomen right upper quadrant	Body	5 cm	Liver, regional lymph nodes	Present	Biopsy
Present study 2019	43	F	Pain abdomen	Body	5 x 4cm	Regional lymph nodes	Present	Radical cholecystectomy with liver wedge resection
	36	F	Pain right upper quadrant, jaundice, fever	Neck	3 x 2.2 cm	Regional lymph nodes	Present	Radical cholecystectomy

Table 4: Comparison of clinical spectrum, radiologicalfeatures and management of Large cell NEC in various studies with the presentstudy

Author	Age/ Sex	Clinical presentation	Tumour location	Tumour size	Metastasis	Calculi	Surgical treatment
Papotti et al 2000 [10]	65/M	Pain abdomen	Fundus	2.5 cm	Liver 4 months after cholecystectomy	Present	Cholecystectomy, chemotherapy and partial liver resection
Lin et al 2010 [11]	65/F	Cushing syndrome	Body	Large ACTH producing mass	Liver, 2 months after surgery	Present	Cholecystectomy and liver wedge resection, patient denied for chemotherapy
Okuyama et al 2013 [12]	64/M	Abdominal fullness	Fundus	2.5 cm	Liver, multiple lymph nodes, bones 22 months after chemotherapy	Present	Biopsy of axillary lymph node and FNAC of gall bladder followed by chemotherapy
Kori et al 2014 [13]	30/F	Pain and mass in right upper abdomen	Fundus, body	9 x 7.5cm	Liver	NA	Radical cholecystectomy
Buscemi et al 2015 [14]	76/F	Pain abdomen	Fundus	1.8 x 1.5 cm	Regional lymph nodes and liver	Present	Cholecystectomy followed by chemotherapy
Ryoichi et al 2016 [15]	86/F	Asymptomatic	Body	2.5 cm	Absent	Present	Cholecystectomy with lymph node dissection
Moris et al 2018 [16]	29/M	Epigastric pain, nausea	Not clear	NA	Absent	Present	Cholecystectomy with liver segmental dissection and lymph node dissection
Present study 2019	51/M	Colicky pain upper abdomen, nausea and vomiting	Fundus, body and neck	8.5 x 7.5 cm	Liver, colon and duodenum	Present	Radical cholecystectomy with partial liver resection with part of duodenum, colon and pancreas

In gall bladder the NETs may arise from the endocrine cells induced by gastric or intestinal metaplasia due to chronic inflammation caused most commonly by calculus. With the advancement of chronic cholecystitis the gall bladder mucosal epithelial cells diverge from their normal differentiation pathway to evolve into gastric or intestinal phenotype. As a matter of fact, most of the published reports of the gall bladder neuroendocrine neoplasms were seen associated with calculi, Similarly in the present study, all the three patients had cholelithiasis. To draw the inference, the gall bladder NETs may arise either from the undifferentiated stem cells or as a result of calculus, however at the same time genetic factors also play important role in oncogenesis and progression of these tumors. [13]

NEC can occur in any part of the gall bladder including neck, body and fundus. The carcinomas in extrahepatic bile ducts can arise at any place within the biliary tree including common hepatic duct and cystic duct. One of the case in this study also showed involvement of cystic duct.

Functionally the neuroendocrine carcinomas can be secretory or non-secretory based on the production of biologically active peptides like serotonin, histamine, substance P and glucagon, prostaglandins, and vasoactive intestinal peptides (VIP). Majority of the NEC are nonsecretory and present with vague symptoms of local disease like pain abdomen, weight loss, nausea, vomiting and weight loss or symptoms due to metastatic disease in case of advanced tumors. In addition to the above symptoms, the functional tumors give rise to the symptoms in relation to the secretion of different peptides. Rarely the hormonal syndromes have been reported in association with NECs which comprises of Cushing syndrome due to ACTH or paraneoplastic sensory neuropathy. [6] All the three patients in this study had non secretory carcinomas and presented with pain abdomen as the major clinical presentation.

NETs are equally distributed among males and females and usually present around an average age of 60 years, however NEC are slightly more common in females with anaverage age of presentation being 65 years and the mean age of 43-83 years. [6,7] present study, the females were affected more as compared to males with male to female ratio of 1:2. The result is in concordance with WHO and

most of the other studies. Two of the patients in this study were under the mean age group and in contrast one patient presented at the age of 36 years which is much younger age of presentation for small cell neuroendocrine carcinoma.

Radiologically, there is no pathognomonic finding of neuroendocrine carcinomas. The imaging techniques like USG, CT scan, MRI and PET-CT can detect the gall bladder lesion, however it is not possible to differentiate NEC from other malignancies preoperatively. However, few of the studies state that if gall bladder tumor present with large hepatic mass or extensive lymphadenopathy at the time of presentation, a differential of NEC should be considered.[14] The definitive diagnosis can be made only by the histopathological examination along with immunohistochemical staining of the resected specimen.

Macroscopically gall bladder NECs are greyish white to yellow usually more than 2 cm in size and mostly polypoid in appearance. However, the size is not definite and may vary from small lesion to huge mass. The lesions measuring 0.3 - 0.5 cm in size usually do not metastasize, while the lesions having size>2 cm often invade liver and may show regional lymph node involvement. All the three cases in the present study were more than or equal to 3 cm and two of them presented as polypoidal mass and one case was ulcero-infiltrative lesion involving liver, duodenum and colon.

It is important to differentiate between large cell and small cell NEC due to their management and prognostic variations. The small cell and large cell neuroendocrine tumors can be differentiated on the basis of histomorphological features. (Table 2). The small cell NECs present as subepithelial growth with tumor cells arranged in nests, cords, trabeculae, and sheets separated by blood vessels along with peripheral palisading and rosette formation. These cells have round to ovoid hyperchromatic nucleus with irregular contour, finely granular salt and pepper chromatin with inconspicuous nucleoli and scant cytoplasm. Nuclear moulding, angioinvasion and perineural invasion is commonly seen. Extensive necrosis is a constant finding. Mitotic figures are frequent and they must be> 20/10HPF as per the current WHO criteria. Immunohistochemical staining shows diffuse positivity for NSE, synaptophysin and scattered positivity for chromogranin A as well as high Ki67 index. In concordance with this both the cases in this study showed similar histopathological and IHC features. The clinical spectrum, radiological features and management of small cell NEC of various studies along with the present study is discussed in Table 3.

Pure Large cell neuroendocrine carcinomas (LCNECs) of the gall bladder are extremely rare. Most of the times LCNECs are seen in combination with other primary histologic components like adenocarcinoma, adenosquamous carcinoma and mucinous carcinoma. As far as we know less than 10 cases of pure LCNECs have been reported in literature till date.[16] (Table 4) The first case of large cell NEC gall bladder was reported by Papotti et al in 2000.[14] Histologically these tumors cells are arranged in organoid pattern with rosette formation. These cells are large in size about 3 times that of small cell type with vesicular nuclei, prominent nucleoli and variable amount of cytoplasm. Mitotic activity is increased. Foci of necrosis is usually present. On IHC the tumor cells exhibit strong expression of neuroendocrine markers like synaptophysin, chromogranin A, and CD56 along with high Ki67 index. In agreement to the characteristic histology the case of large cell NEC in the present study showed similar findings with positive staining for synaptophysin, chromogranin and negative staining for cytokeratin. Ki67 index in this case was 75-80%.

Prognosis of neuroendocrine carcinomas of gall bladder either of small or large type is poor and this poor prognosis is due to non-specific, inert clinical presentation, lack of screening test for early detection and also lack of pathognomonic radiological features. Poor prognostic factors include poorly differentiated type of NEC, increased mitotic activity, high ki67 index and tumor invasion. Around 40-50% of the patients have disseminated disease at the time of presentation.[6] The prognosis worsens further in the patients with unresectabletumors. According to the SEER database the survival rates for all gall bladder neuroendocrine carcinomas are low with 1-year survival rate of 43-45%, 2-year 30-33%, 3-year 28-31%, 4-year 22-26% and 5-year survival rate of 22-25% respectively.[16] All the three patients in the present study are referred to chemotherapy following surgery. All of them are alive and no adverse event has been reported till date.

Due to the rarity of these carcinomas there is only little perception about the biological behavior and at present there are no definite management protocols. However, multidisciplinary approach comprising of surgery followed by chemotherapy and radiotherapy is the preferred treatment of these tumors. Surgery may include simple cholecystectomy, radical cholecystectomy, regional lymph node dissection and partial liver resection according to the extent of invasion. In patients with the disease limited to mucosa or submucosa only cholecystectomy is required, however in case of local invasion without any distant metastasis, lymph node dissection and segmental liver resection is required along with cholecystectomy. Prognosis is better in patients in whom surgical procedure is followed by adjuvant chemotherapy. The chemotherapeutic agents commonly used in NECs comprise of cisplatin, 5fluorouracil, etoposide and doxor ubicin. Patients with small cell carcinoma respond well to chemotherapy as compared with large cell carcinoma. The patients with metastatic disease, in whom other treatment options play little role respond well to receptor radiotherapy known as biotherapy using somatostatin analogues.

4. Conclusion

Neuroendocrine carcinomas are rare and aggressive variants of the gall bladder carcinomas. The ccombativeness of the tumour is due to lack of specific clinical symptoms as well as radiological findings to detect these tumours pre-operatively. The patient may be totally asymptomatic leading to incidental detection of the disease or may present with metastatic disease involving liver, lymph nodes and other adjacent organs leading to poor prognosis. Histopathology of the resected specimen and immunochemical analysis remain the main stay of diagnosing these malignancies. The improved survival rate is seen with multimodality treatment protocol which includes surgery followed by adjuvant chemotherapy in the patients with locally invasive disease. Systemic chemotherapy and radiotherapy remains the treatment of choice in patients with inoperable tumor, in case of metastatic malignancy or in case of the tumors with positive margins. The large cell NEC does not respond well to chemotherapy so the prognosis is even poorer. However, due to decreased incidence of the disease and only few studies available, there are no definite management guidelines. More effective perception of the biological behavior of the disease and and extensive literature are required to understand the overall prognosis and to define a universal treatment protocol in order to improve the quality of life of the patients.

5. Source of funding

None.

6. Conflict of interest

None.

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