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Neuroendocrine Carcinoma of Gall Bladder - A Case Series and Review of Literature

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Abstract: ***Introduction**: Neuroendocrine carcinoma (NEC) of the gallbladder is an exceptionally rare and aggressive malignancy, representing only 0.2% of all gastrointestinal and hepatobiliary NECs. Due to its rarity, evidence - based guidelines for diagnosis and treatment remain undefined. **Methodology**: We conducted a retrospective analysis of NEC of the gallbladder cases diagnosed at our institute from 2005 to 2023. Clinical records, imaging, histopathological reports, and treatment details were reviewed to characterize presentation, management, and outcomes. **Results**: A total of 10 cases were identified. The median age at diagnosis was 48.5 years (range 18–85), with a female predominance (M: F = 1: 4). Most patients presented with abdominal pain and weight loss. Imaging with contrast - enhanced CT revealed locally advanced disease in 6 patients and metastatic disease in 4. One patient was incidentally diagnosed post - cholecystectomy. Diagnosis was confirmed via histopathology and immunohistochemistry, with synaptophysin and chromogranin positivity in 90% and 80% of cases respectively. The Ki - 67 index was >80% in 9 cases. Six patients received etoposide - platinum chemotherapy, with a median progression - free survival of 5.5 months. Progression included hepatic dysfunction, brain metastasis, and radiological advancement. **Conclusion**: Gallbladder NECs are typically diagnosed at an advanced stage due to non - specific symptoms. The absence of standardized treatment protocols underscores the importance of individualized, multidisciplinary approaches. Further research and clinical trials are warranted to establish optimal therapeutic strategies.*

Keywords: Neuro - endocrine Carcinoma, Gall Bladder, Rare malignancy, Immunohistochemistry, Multidisciplinary management

1. Introduction

Neuroendocrine tumour (NET) is a rare neoplasm with the incidence of about 5.25 per 100, 000 [1]. The incidence of gallbladder NET was less than 0.74/100, 000 according to Surveillance, Epidemiology and End Result (SEER) database [1]. Being a poorly differentiated NET, neuroendocrine carcinoma (NEC) of gall bladder is even less. Gall bladder NECs comprise only 0.2% of all gastrointestinal/hepatobiliary NECs [1]. Because of the rare nature, there are no definite treatment guidelines for the management of such tumours.

2. Methodology

A retrospective analysis of all cases of NEC of gall bladder registered in our institute from 2005 to 2023 was done. Case files were retrieved and all clinical, radiological, histopathological and treatment records were reviewed.

3. Results

Ten cases of NEC of gall bladder were registered in this period. The median age of presentation was 48.5 years (range 18 to 85 years) with male: female ratio of 1: 4. The most common presenting complaints were abdominal pain and weight loss. Staging was done using contrast enhanced Computed Tomography (CECT) scans of the thorax, abdomen and pelvis. Six of the ten patients presented with locally advanced disease with extensive nodal disease and four had metastatic disease at presentation. One of the patients had been operated for suspected chronic cholecystitis and cholelithiasis at a different centre and was incidentally diagnosed. The remaining underwent trucut biopsy followed by histopathological examination and immunohistochemical (IHC) staining. Synaptophysin (SYN) and Chromogranin (CGA) were the most consistent IHC markers, found in 90% and 80% respectively, MIB index was >80% in nine out of the ten patients. Six of the ten patients received chemotherapy with Etoposide - Platinum combination, three patients were not fit for chemotherapy and advised best supportive care and one patient refused chemotherapy. Among patients receiving chemotherapy, median progression free survival (PFS) was 5.5 months. Among the 6 patients receiving chemotherapy, 3 patients had clinical progression in the form of hyperbilirubinemia, one patient developed convulsions and was diagnosed as brain metastasis on imaging while 2 patients had radiological progression without clinical progression. One patient received second line chemotherapy with Irinotecan.

Table 1: Clinical and Pathological Features, Treatment and Outcomes of Patients of Neuroendocrine Carcinoma of the Gall Bladder

S No.	Age	Sex	ECOG PS	AJCC Stage	IHC			Treatment	Outcome
					SYN	CGA	MIBI		
1	18	F	1	III	+	+	80	4 x Cisplatin - Etoposide	PFS = 5 months. Progressive hyperbilirubinemia
2	56	F	4	IV	+	-	90	Unfit for chemotherapy	Best supportive care
3	56	F	1	IV	-	+	90	6 x Cisplatin - Etoposide	PFS = 5.5 months. Radiological progression.
4	85	M	4	III	+	+	100	Unfit for chemotherapy	Best supportive care
5	70	M	3	III	+	-	100	Unfit for chemotherapy	Best supportive care

6	45	F	1	III	+	+	40	Radical Cholecystectomy, refused adjuvant	PFS = 3 months. Progressive hyperbilirubinemia → Drainage
7	26	F	2	III	+	+	80	6 x Carboplatin - Etoposide	PFS = 6 months. Progressive hyperbilirubinemia → Stenting
8	35	F	1	IV	+	+	90	6 x Carboplatin - Etoposide	PFS = 6 months. Radiological progression.
9	32	F	2	IV	+	+	90	3 x Carboplatin - Etoposide	PFS = 3 months. Brain mets → WBRT
10	52	F	1	III	+	+	80	4 x Carboplatin - Etoposide	PFS = 3 months. Radiological progression.

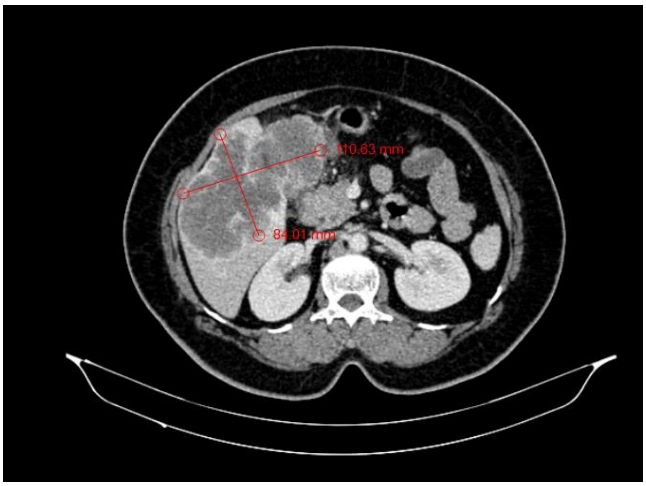

Figure 1: CECT Abdomen showing a Gall Bladder mass

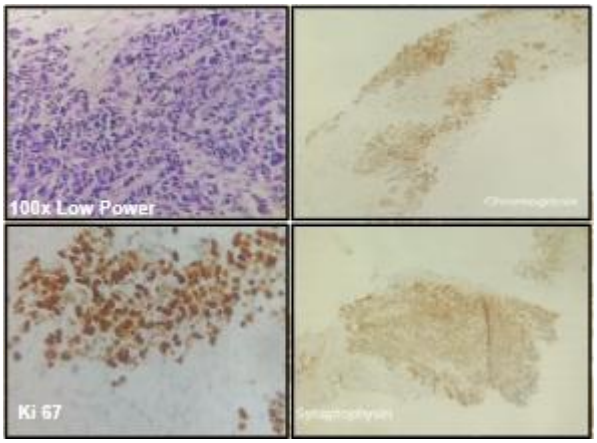

Figure 2: Histopathology and IHC findings in a case of NEC Gall Bladder

4. Discussion

NEC of the gallbladder is a rare and aggressive cancer that arises from neuroendocrine cells. According to the World Health Organization (WHO) 2022, NETs of the gastrointestinal tract are classified according to the rate of tumour proliferation, using mitotic counts or the ki - 67 marker index [2, 3]. NETs are generally divided into well differentiated NETs and poorly differentiated NET or NEC. Well differentiated NETs are further graded as Grades 1, 2 and 3 based on Ki 67 values (less than 2, 3 to 20 and more than 20 respectively) and mitotic index (lee than 2, 2 to 10 and more than 10 respectively per 10 high power fields) whereas NEC are by definition are poorly differentiated with Ki 67 more than 20 [2, 4, 5].

The clinical manifestations are non - specific. The most common presentation is a right upper quadrant discomfort, including pain with distention and tenderness.

Ultrasonography, Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) of the abdomen can detect solid masses of gallbladder but are unable to distinguish from other types of gallbladder carcinoma. They are also essential for the TNM staging and formulation of treatment plan. Confirmatory diagnosis of gallbladder NEC relies on histopathological examination and IHC staining. Common IHC markers are Chromogranin A and synaptophysin, with positivity rates of 91.9% and 84.8% respectively [6].

There is no consensus of treatment of gallbladder NEC. Surgical management remains a first - line consideration for early - stage tumours with simple cholecystectomy sufficing for early stage disease [7]. For more advanced operable tumours, radical cholecystectomy including local lymph node dissection should be pursued [8]. For patients with distant metastasis, surgical treatment remains controversial. The platinum - based chemotherapy regimens according to guidelines of lung small cell carcinoma were used in treatment of NEC. The most recommended therapy is cisplatin or carboplatin plus etoposide [8, 9]. Carrera et al. reported that the use of cisplatin with etoposide improved four - month survival compared to other chemotherapy regimens [10].

The prognosis of gallbladder NEC is very poor. Duffy et al. reported that the median survival of gallbladder NEC was 9.8 months, lower than the median survival of gallbladder carcinoma [5].

5. Conclusion

Due to rarity of cases, variable age of presentation, lack of specificity of presenting complaints, diagnosis is often made at advanced stages when the disease is no longer amenable to surgery. There are no standard guidelines for screening or management of NEC of gall bladder. No prospective randomised controlled trials have been done for this entity. Published literature is in the form of case reports and series. Multidisciplinary tumour board discussions should be considered to determine optimum management of such patients.

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