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Case Report

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Neuroendocrine Carcinoma of Gall Bladder: A Case Study

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ABSTRACT

Neuroendocrine Carcinoma of Gallbladder is a rare tumor, which is heterogenous neoplasm originating from neuroendocrine cells, which secrete neurotransmitter. Among all theneuroendocrine neoplasms, gallbladder neuroendocrine neoplasm prevalence is 0.5% accounting for approximately 2.1% of all the gallbladder tumors.

Case Presentation As gallbladder neuroendocrine neoplasm is a rare lesion it is seldom seenin clinical practice, there is a limited availability of review reports and it is therefore often considered only as a case study.

It is difficult to distinguish gallbladder neuroendocrine neoplasms from other gallbladder diseases using imaging diagnostic techniques.

We here report a case of 55 years old female presenting with right upper quadrant and epigastric pain and eventually diagnosed with mixed cell neuroendocrine carcinoma of gallbladder.

Conclusion Therefore to overcome inherent risks or shortfalls of traditional surgery, early detection, diagnosis and treatment of gallbladder neuroendocrine neoplasms are required to improve patient longevity.

Key Words: *Neuroendocrine, gallbladder, neuroendocrine tumor, surgery*

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INTRODUCTION

Neuroendocrine Tumors (NET's) are a group of neoplasms that originate from neuroendocrine cells present in various organs but more commonly found in GI tract, Lungs and thyroid [1].

These cells perform essential biochemical functions such as the uptake of amine precursors, decarboxylation and the release of bioactive peptidehormones and nerve mediators [2].

Aiming to investigate the characteristics of gallbladder neuroendocrine carcinoma (NEC), we present this case report and review the previous published articles. 55 years old female normotensive, non diabetic female patient presented with dull aching pain in epigastrium and right hypochondrium for 2 months. There was no history of fever or jaundice. Abdomen was soft and non-tender on examination.

Ultrasound examination demonstrated distended gallbladder with the heterogenous exophytic lesion of mixed echogenicity in gallbladder with associated asymmetric Gall bladder wall thickening.

On gross specimen examination (Fig.1), gallbladder measured 7X5X2 cms. Cut section showed a whitish firm growth at the fundus measuring 2X2 cms.

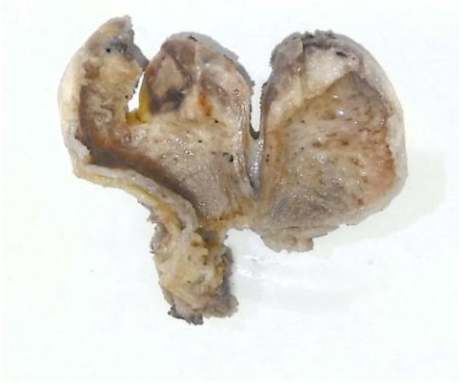

Fig.1: Cut section of gallbladder showing a tumor (whitish firm growth) arising from fundus.

On microscopic examination (Fig.2), a tumor arising from gall bladder mucosa was observed with a large area of tumor depicting neuroendocrine differentiation and was arranged in nests and chords in a desmoplastic stroma. Brisk mitosis was also observed tumor cells arranged in sheets and island in a desmoplastic stroma .Tumor cells were spindle and round to oval having scant cytoplasm with pleomorphic nuclei having speckled nuclear chromatin with nuclear hyperchromasia. The tumor was infiltrating entire thickness of the wall of gallbladder and extending into the surrounding fat. Tumor revealed large areas of hemorrhage and necrosis.

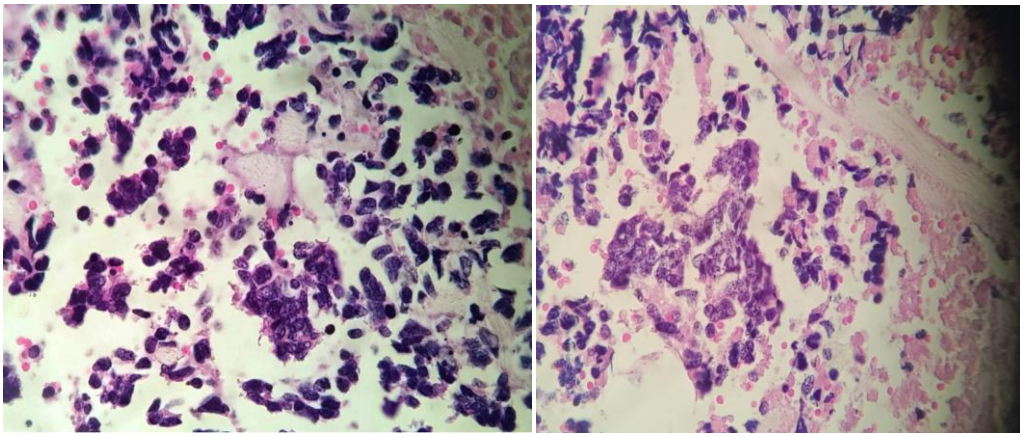

Figure 2: Histopathological examination H and E, x 20. Microscopic findings were of mixed large and small cell neuroendocrine carcinoma.

On Immunohistochemistry tumor was Negative for CK 7 and CK 20 (Fig.3 and Fig.4) but Positive for chromogranin (Fig. 5)

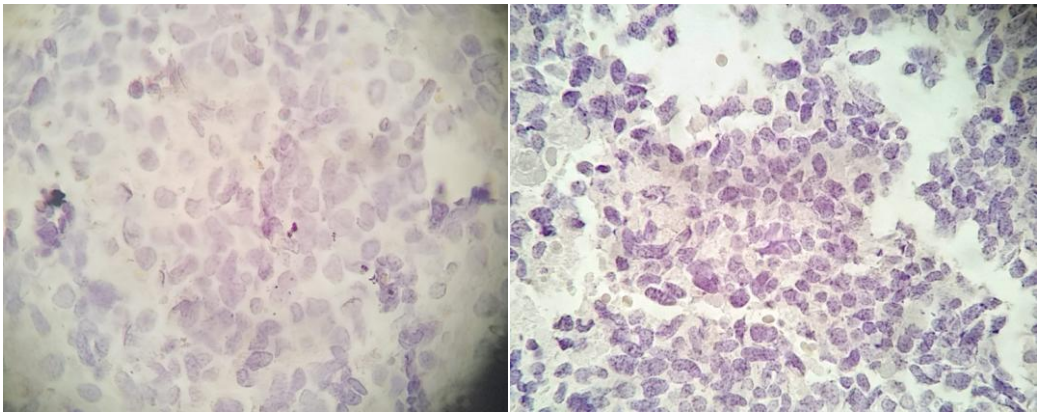

Figure 3: CK7 **Figure 4:** CK20

Immunohistochemistry staining for CK7 (fig.2) and CK20 (fig.3) were negative.

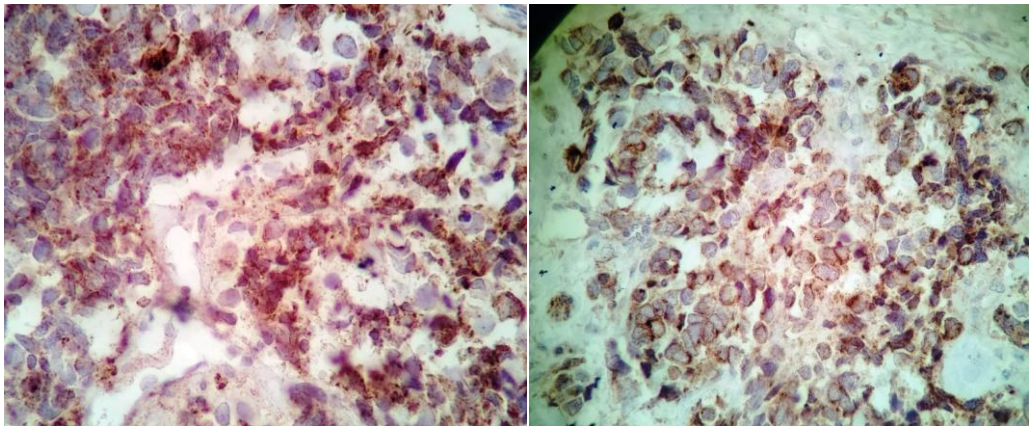

Figure 5: Immunohistochemical staining for Chromogranin A, revealed positive expression of Chromogranin A.

DISCUSSION

To identify the root cause of the GB-NEN, a thorough examination and understanding of the cellular nature of the disease is important. In the process of examination minimal neuroendocrine cells can be found on the gallbladder mucosa, if any exist in this space [3, 4 & 5].

Further GB-NEN etiological identifiers may be as follows:

1) The undifferentiated gallbladder stem cells differentiate into neuroendocrine cells.
2) The presence of gallbladder stones results in Chronic inflammation of the G.B mucosa causing intestinal epithelium or gastric metaplasia, which are considered to be pathological. In an advanced stage, this inflammation produces neuroendocrine cells at the lesion site leading eventually to development of GB-NEN [4, 6 & 7].
3) In certain situations the gallbladder adenocarcinoma function switches to a neuroendocrine one, resulting in chronic inflammation of gallbladder tissues and formation of stones, further exacerbating the other risk factors for gallbladder adeno carcinoma [8].

Pathological classification:

There are 3 pathological classifications of GB-NEN:

- Carcinoid or typical carcinoid (low grade)
- Atypical carcinoid (moderate grade)
- Small cell carcinoma (high grade)

These classifications are based on GB-NEN histopathological structure, cell morphology and degree of differentiation, mitoticactivity and necrosis and biological behavior [9].

GB-NEN cells have small nucleoli, granular chromatin and relatively consistent tumor cell morphology and are rich in interstitial blood vessels [10].

According to the classification criteria of digestive system tumors by the World Health Organization in 2010, the well-differentiated NET's include grades G1 and G2 and poorly differentiated NET (G3). Neuroendocrine carcinoma is further classified based on the tumorcell size into large or small cell .G1 contains both the neuroendocrine carcinoma and adenocarcinoma tumor and is therefore identified as a mixed gland neuroendocrine carcinoma [9].

Well differentiated NET's are well circumscribed with relatively uniform cells and nuclei with granular cytoplasm and stripped chromatin. Most of them secrete neuro-secretory granules and express markers such as synaptophysin and chromogranin A. There are some tumors that specifically secrete hormones such as insulin, glucagon, gastrin and somatostatin etc.

Poorly differentiated NEC's on the other hand have non-uniform cells with irregular nuclei and less cytoplasm granularity. They can still have some immune reactivity but not as much as well differentiatedNET's.

Clinical Features

There are no specific symptoms and signs that are characteristics for gallbladder NEC's. The clinical manifestations of gallbladder NEC vary. In general, the main complaint is the right upper quadrant discomfort/pain, nausea and vomiting and positive Murphy's sign. Some patients present with loss of appetite and weight loss [11].

However the pain is indistinguishable from cholelithiasis.

DIAGNOSIS

The diagnosis of GB-NEN prior to surgery remains difficult. Currently, tumor markers and imaging examination such as ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI), are used.

All these imaging techniques detected masses in gallbladder and thickening of gall bladder. Most of the cases of NEC's are located in the gallbladder body. Most of the times NEC cannot be distinguished from other types of gallbladder cancers just based on imaging studies.

A definitive diagnosis of gallbladder NEC's is made only based on histopathology and immunohistochemical staining. Common biomarkers of Immunohistochemistry are Chromogranin A and Synaptophysin with positive rate of 91.9% and 84.8% [12]. In addition histopathology determine the tumor grading and staging.

At present, the origin of GB-NEN is unclear, the clinical manifestations are atypical and the majority of Laboratory and imaging examinations provide no specificity.

The treatment options for gallbladder NEC vary based on the stage of tumors early in situtumors usually responded well to cholecystectomy alone (13). But late stage tumors need radical surgeries along with dissection of nodes and even removal of some close metastatic lesions (14). As most of the patients presents in advanced stages, they need concomitantchemoradition. Despite all above treatment options, gallbladder NEC still has very high mortality with poor prognosis.

CONCLUSION

The current case report demonstrates that GB-NEN is a relatively rare gallbladder lesion, unique in presentation and often relayed as a case study.

Therefore early detection, correct diagnosis and reasonable treatment of such tumourshelps in extending the quality of life of the affected patients. Due to low incidence and availability of studies, there is no uniform standard treatment identified for treating GB-NEN. Because of the rarity of the disease we need more research to diagnose these patients early and come up with a standardized treatment plan.

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