Case Report

Gallbladder neuroendocrine carcinoma: A rare entity case report with review of literatures

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ABSTRACT

Neuroendocrine neoplasm (NEN) of the gallbladder (GB) is an extremely rare malignancy, accounting for only 0.2% of all NENs. GB-neuroendocrine carcinomas (NEC) are difficult to differentiate from adenocarcinoma on routine imaging. These tumors do not present with specific symptoms. Histopathological examination is the gold standard for the diagnosis of GB-NEC. They have worse outcomes than GB-adenocarcinoma and have disseminated metastases at the time of diagnosis. We present the case of a 65-year-old woman who presented with a GB mass and abdominal pain. Histopathological and immunohistochemical findings revealed GB-NEC.

Key words: Carcinoma, Gallbladder, Neuroendocrine neoplasm, Rare malignancy

Neuroendocrine cells are specialized cells that originated from neural crest cells. These cells are distributed throughout the body in different organs and secrete hormones. The neuroendocrine neoplasms (NEN) are a diverse group of tumors, commonly seen affecting the gastrointestinal tract, pancreas, and bronchopulmonary system, arising from neuroendocrine cells or Kulchitsky cells. The incidence of NEN in the gallbladder (GB) and biliary system is extremely rare, accounting for only 0.2% of all NEN and 2.1% of all GB tumors [1-3]. In GB, any part of the neck, body, or fundus can be involved by NEN. Neuroendocrine carcinoma (NEC) occurs more commonly than neuroendocrine tumor in the GB [4]. They are relatively more common in females and occur in the 6th–7th decades of life [5]. GB-NEC have a worse prognosis compared to GB adenocarcinoma, and >50% of the patients present with disseminated disease at the time of diagnosis [6,7]. In India, very few cases of GB-NEC have been reported till now [8-10].

We report a case of GB carcinoma reported as NEC with a review of the literature.

CASE REPORT

A 65-year-old woman presented with dull aching abdominal pain and distension for 10 days. There was no history of fever, jaundice, weight loss, or hematemesis. She was diabetic and hypertensive.

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On physical examination, a hard lump was palpated at the right hypochondrium. On general examination, no pallor/icterus/edema was noted. Respiratory, cardiovascular, and central nervous system examinations were within normal limits.

Preliminary laboratory investigations showed mild anemia, high serum bilirubin (3.2 mg/dL), transaminases (serum glutamic pyruvic transaminase-75 U/l, serum glutamic-oxaloacetic transaminase-62 U/L), and cancer antigen 19–9 (48 U/mL). Alkaline phosphatase was normal (52 IU/L).

Computed tomography (CT) scan of the whole abdomen reveals a large necrotic mass replacing the GB. There was extensive hepatic infiltration involving segment IVb, V, VI, and I. The mass was also infiltrating the pyloric antrum, duodenum, head, and uncinate process of the pancreas. The right branch of the portal vein was not well visualized. No significant biliary dilatation was noted. The mass measures approximately 10.3 × 10.2 cm. There were a few necrotic portal and peripancreatic nodes (no CT image was available). No ascites was seen. The radiological diagnosis of GB carcinoma with extensive hepatic infiltration and infiltration of other adjacent structures, along with adenopathies, was made. CT scan of the thorax findings were within normal limits with no pulmonary secondaries. As the tumor was locally advanced, an ultrasound-guided fine-needle aspiration cytology and trucut biopsy of the GB mass were performed elsewhere and were reported as suggestive of poorly differentiated carcinoma.

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We received the block and slides for review and further evaluation. The sections reveal tissue infiltrated by malignant cells in sheets, acini, and a trabecular pattern. The cells have a high nucleocytoplasmic ratio, scant eosinophilic cytoplasm, ovoid to elongated hyperchromatic nuclei with moulding and inconspicuous nucleoli. Brisk mitoses and necrosis were seen (Fig. 1). The immunohistochemistry (IHC) revealed punctate positivity of pancytokeratin, cytoplasmic positivity of synaptophysin, nuclear positivity of INSM1, negative staining for CK7, CK20, and glypican 3. The proliferation index (Ki67) was very high 75% (Fig. 2). The patient was given the diagnosis of NEC of the GB. The patient is currently on 2 cycles of platinum-based chemotherapy (Cisplatin + Etoposide).

DISCUSSION

Neuroendocrine cells are very rare to non-existent in GB; however, their existence can be seen in cholelithiatic GB. The definite etiology of GB-NEN is not known. Some studies proposed that GB epithelium can undergo intestinal metaplastic changes in the presence of chronic inflammation and then produce neuroendocrine cells, giving rise to NEN at the lesional site [11,12]. Some NENs are associated with von Hippel–Lindau syndrome (VHL) and multiple endocrine neoplasia type 1. In most of the GB-NECs, p53 mutation and inactivation of the RB1/p16 pathway have been found. Previous studies revealed that activation of the epidermal growth factor receptor can upregulate downstream signaling protein kinase B, and its accumulation is associated with poor prognosis in GB-NEN [13].

The signs and symptoms of GB-NEN are non-specific. The patients may present with abdominal pain and distension, weight loss, jaundice, and ascites.

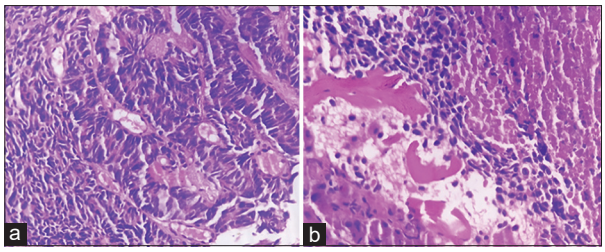

Figure 1: (a) Tumor cells arranged in sheets and acinar pattern, (b) Necrosis (Hematoxylin and Eosin stain, ×400)

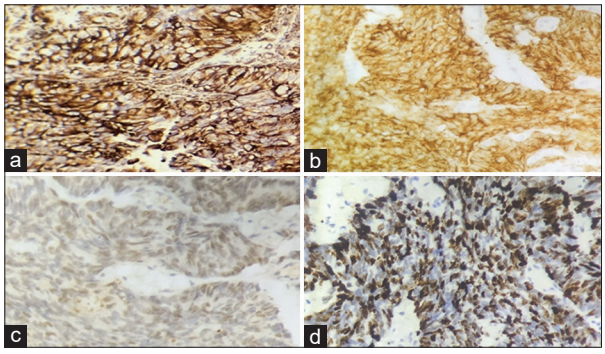

Figure 2: (a) Pancytokeratin, (b) Synaptophysin, (c) INSM1, (d) Ki 67 (immunohistochemistry, ×400)

Traditional imaging methods are not sensitive to the diagnosis of GB-NEC. This cannot differentiate between adenocarcinoma and NEN [14]. The gold standard for the diagnosis of GB-NEN remains histopathological examination followed by IHCs. Neuroendocrine cells show immunoreactivity to synaptophysin, chromogranin, INSM1, and cytokeratin. Some NEN that are VHL-associated may show inhibin immunoreactivity, unlike sporadic cases [15].

Clinical symptoms are non-specific; they present mostly with right upper quadrant abdominal pain and discomfort. There are no particular tumor markers specific for GB-NECs. Serum chromogranin A, carcinoembryonic antigen, carbohydrate antigen (CA)-125, and CA-19-9 have all been shown to be high in GB-NEC on occasion and are said to be associated with poorer prognosis [16].

The prognosis of GB-NEC is poorer than that of GB adenocarcinoma. Mostly present with lymph node (LN) and liver metastases at the time of diagnosis. Moreover, GB-NEC has a higher rate of N2 LN metastases compared to adenocarcinoma [17]. According to Duffy *et al*., in contrast to 10.3 months survival for patients with GB adenocarcinoma, the median survival for GB-NEC was 9.8 months [18].

Surgical resection is the first-line management for localised GB-NEC. Radical cholecystectomy with histopathologically negative resection margins and negative lymph nodal metastatic status prolongs the patient's survival. Chemotherapy should be given to patients who are not eligible for surgery.

It is important to differentiate it from GB-adenocarcinoma, which is the closest differential diagnosis. Their treatment is totally different. Other differentials that can be considered are poorly differentiated hepatocellular carcinoma, hepatic flexure colon adenocarcinoma involving GB, and metastatic carcinomas. Advanced stages of GB-NEC patients receive platinum-based chemotherapy, while adenocarcinomas are treated with gemcitabine-based chemotherapy. According to Kim *et al*., a patient with GB-NEC identified at the T3N1M0 stage received laparoscopic radical cholecystectomy and combination chemoradiation therapy; during the 14-month follow-up period, there was no sign of recurrence [19]. According to Elahi *et al*., a 52-year-old woman with GB-NEC that included the LNs and omentum had a laparoscopic radical cholecystectomy. She underwent chemotherapy and radiation therapy following the procedure, and she lived for more than 46 months [20]. Poor survival is independently linked to older age, unmarried status, large tumor size (>5 cm), positive margins, and distant surveillance, epidemiology, and results stage. There is an ongoing debate on the possible survival advantage of lymphadenectomy for patients. Post-operative adjuvant chemotherapy based on platinum may increase survival. More research is required to determine the effectiveness of additional therapies, such as immunotherapy, targeted therapy, and somatostatin analogues [16].

CONCLUSION

GB-NEN is extremely rare and is associated with a poor prognosis. Due to its rarity, data on its clinical information, etiology, and treatment modalities are limited. GB-NEN cannot be differentiated from GB-adenocarcinomas on routine imaging techniques. Hence, its diagnosis solely relies on histopathological examinations. Patients with advanced GB-NEC treated with surgical resection combined with chemotherapy/radiotherapy may have a better prognosis than those treated with surgical resection alone.

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