Gallbladder: A rare primary site for small cell carcinoma

Neuroendocrine tumors (NETs) are an extremely rare entity in gallbladder (GB), occurring in approximately 0.5% cases of NETs from all sites. In the present case report, a 42-year-old male presented with recurrent right upper quadrant pain for 2 months. Abdominal ultrasound revealed a small nodular swelling in the GB. On aspiration cytology that appeared as individual small tumor cells mostly in dispersed population and frequent nuclear molding within cell aggregates in a necrotic background. The patient was diagnosed as NET of GB. Histopathology revealed; uniform small rounded cells arranged in peritheliomatous pattern with intervening areas of massive necrosis. Nuclear molding, salt-pepper nuclear chromatin and frequent mitoses were also evident. Immunohistochemistry with chromogranin confirmed the diagnosis of small cell carcinoma.

Key words: Chromogranin, gallbladder, neuroendocrine tumor, small cell carcinoma

INTRODUCTION

Neuroendocrine tumors (NETs) commonly arise in gastrointestinal tracts and bronchi; but rarely occur in gallbladder (GB). Depending upon biological behavior, NETs are broadly classified as well-differentiated NETs, also called carcinoid tumors; well-differentiated neuroendocrine carcinomas, which encompasses atypical carcinoid and small cell carcinoma; and poorly differentiated large cell or high-grade neuroendocrine carcinomas. High-grade neuroendocrine carcinomas are distinguished from typical carcinoids (<2 mitoses/10 hpf) by virtue of necrosis and increased mitoses (>10/10 hpf). NETs in GB comprise approximately 0.5% of all neuroendocrine neoplasms and ~2% of all GB cancers. Because of its rarity, variable clinical presentation and uncertainty in its behavior NETs originating from GB remains an enigmatic disease.

Here, we report a rare case of small cell carcinoma in GB affecting a 42-year-old male.

CASE REPORT

A 42-year-old man presented with right upper quadrant pain with progressive loss of weight since past 2 months. At presentation, the patient was absolutely normal on general examination. His full blood count, liver function tests, prothrombin time, chest X-ray — everything was unremarkable, except mildly elevated alkaline phosphatase level of 173 U/L.

Abdominal ultrasound demonstrated a 15 mm × 11 mm mixed echoic mass at the neck of GB without any residual lesion in the liver or any features of biliary obstruction.

Fine-needle aspiration cytology was performed from the lesion under ultrasound guidance, which showed round to ovoid tumor cells arranged in loose clusters and also dispersed singly. Within the cohesive aggregates, nuclear molding was easily discernible. Individually dispersed tumor nuclei often featured characteristic smearing artefacts. Well-preserved tumor cells had high nucleo-cytoplasmic ratio with a mildly irregular nuclear contour, finely granular uniformly dispersed chromatin and absent nucleoli in a background of granular necrotic debris [Figure 1]. Provisional diagnosis was provided as NET of GB, with a suggestion of histopathological confirmation.

Then the patient went under knife and the entire GB along with its mass was resected out. Histopathological examination of the sections showed tumor cells arranged in widened trabecular...
and peritheliomatous pattern with massive areas of necrosis intervening between them. The nuclei were uniform, small, round to oval in shape; with finely granular classic “salt-pepper” chromatin, absent nucleoli and scanty cytoplasm. Mitotic counts were numerous, counting >20/10 hpf [Figure 2]. All these histopathological findings pointed toward the diagnosis of small cell carcinoma.

Immunohistochemical stains for chromogranin A revealed coarse granular cytoplasmic positivity [Figure 3]; further confirming the neuroendocrine origin of the tumor cells and the diagnosis of small cell carcinoma.

The patient was postoperatively treated with adjuvant chemotherapeutic regimen prescribed by medical oncologists and remained relatively symptom-free for next 6 months on follow-up.

**DISCUSSION**

Neuroendocrine tumors are relatively rare neoplasm, occurring in 2 cases per 100,000 persons and account for 0.5% of all malignancies.[5] Majority (66%) of these tumors arise in the gastrointestinal tract and the second most prevalent site is the bronchopulmonary system (31%), followed by less frequent locations like ovaries, testes, pancreas and hepatobiliary system, including GB.[6] NETs in GB represent 0.5% of all NETs and approximately 2% of all GB tumors.[4,7]

According to current WHO classification,[2,3,8] NETs are subdivided into:

- Well-differentiated NETs, also referred to as typical carcinoid (WHO1), exhibiting a benign behavior or uncertain malignant potential
- Well-differentiated neuroendocrine carcinoma, caters entities like atypical carcinoid, small cell carcinoma (WHO2); and
- Large cell neuroendocrine carcinomas or poorly differentiated neuroendocrine carcinoma, of high-grade malignancy (WHO3).

In most cases of small cell carcinomas, patients typically present with recurrent upper quadrant pain. Other uncommon presentations include abdominal mass, weight loss and ascites. It is usually a nonfunctional tumor without any clinical manifestations secondary to secretion of biologically active peptides.[9‑11] Similarly, the current case presented with only abdominal pain without any relevant paraneoplastic symptoms. Moreover, small cell carcinomas are often discovered late in the disease process when adjacent organs are infiltrated, or the biliary drainage is compromised. Consequently, the prognosis is poor with survival rates worse than other GB malignancies.[9‑11]

To their respective case-series on GB NETs undertaken by Pitt et al[12] and Nishihara and Tsuneyoshi[13] opined, “65 years” as the average presenting age for small cell carcinomas, which is preponderant in females and are almost always associated with stones. In contrast, the discussed patient was male with 42 years of age, which is much lower than the average age of presentation.
for small cell carcinoma and neither was he having any forms of cholelithiasis or choledocholithiasis.

Cytologically, small cell carcinomas show, loose clusters as well as dispersed population of individual tumor cells having high nuclear/cytoplasmic ratio, ovoid to irregular nuclear contour, finely granular and uniformly distributed chromatin yielding the classic “salt and pepper” quality with inconspicuous nucleoli. Within the cohesive aggregates, well-developed nuclear molding is evident. Due to the fragility of malignant nuclei, chromatin streaks are commonly visualized in aspirated smears.[11] These cytopathological features were promptly recapitulated in the present case.

Classic architectural patterns of small cell carcinoma include nesting, trabeculae, peripheral palisading, and rosette formation. Sheet-like growth with peritheliomatous (surrounding the blood vessels) distribution of tumor cells and massive areas of geographic necrosis, as observed in the current case, is also common. Tumor cells are usually less than the size of three small resting lymphocytes and have round to ovoid to spindled nuclei, finely granular nuclear chromatin and nucleoli are absent or inconspicuous with scant cytoplasm. Cell borders are indistinct and nuclear molding is obvious.[14,15] Mitotic count is very high. By WHO definition, small cell carcinomas contain >10 mitoses/2 mm² area.[5]

Immunohistochemical staining shows strong positivity for neuroendocrine markers, like chromogranin A and synaptophysin. In comparison to other NETs that are diffusely positive for neuroendocrine markers, small cell carcinomas show more focal staining.[16,17] Similarly, the neoplastic cells in the discussed case stained strongly with chromogranin A for cytoplasmic granularity.

Therapeutic options are often limited due to the advanced nature of this disease at diagnosis. Surgical excision remains the best curative option. However, the need for a radical excision and the extent for removal of surrounding tissue are debatable. In patients unsuitable for curative surgery, different chemotherapy regimens are described. Moskal et al. depicted that patients treated with surgical excision and concomitant adjuvant chemotherapy has a better median survival of 13 months, rather than a mere 4.5 months in untreated patients.[18] The current patient was treated with excision followed by adjuvant chemotherapy and remained relapse-free on 6 months follow-up.

CONCLUSION

Finally, to conclude, small cell carcinoma of GB is an exceptionally rare malignancy. Despite the use of combined anatomic and functional imaging a precise diagnosis of NET is quite difficult. Provisional diagnosis can be rendered by cytopathological findings and confirmed by histopathological examination, which corroborates well with the distinctive staining pattern with neuroendocrine markers. Small cell carcinoma has strikingly poor prognosis. Early diagnosis with prompt surgical intervention provides best long-term outcome. Adjuvant chemotherapy provides a definite survival advantage to the patient, but is without a well-defined standard of care protocol.

REFERENCES