NEUROENDOCRINE CARCINOMA OF STOMACH - A CASE REPORT

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Abstract:
Carcinoid tumors are neuroendocrine neoplasms which are amine precursor uptake decarboxylase (APUD)omas that arise from enterochromaffin cells present throughout the gut. The majority are found in the gastrointestinal tract and more than 40 percent occur in the small intestine. Gastric carcinoids can be associated with endocrine cell hyperplasia, chronic atrophic gastritis, Zollinger-Ellison Syndrome (ZES). These tumors secrete discrete bioactive substances producing characteristic clinical features and immunohistochemical patterns. Neuroendocrine carcinoma are the malignant counterpart of carcinoid tumor. Here we report a case of neuroendocrine carcinoma of stomach in a 40 year old female presenting with recurrent vomiting, pain abdomen and mass per abdomen. Subtotal gastrectomy was done. Histopathological examination revealed features of Large cell neuroendocrine carcinoma which showed positivity for Chromogranin and Neuron specific enolase (NSE) immunohistochemically.

INTRODUCTION:
Neuroendocrine neoplasms, defined as epithelial neoplasms with predominant neuroendocrine differentiation arise in most organs of the body. 54% of all neuroendocrine tumors occur in Gastrointestinal tract (GIT). Their prognosis varies according to the grade of the tumour. Biological behavior, treatment and prognosis are distinctly different from other types of malignancies that occur in GIT. Large cell Neuroendocrine carcinoma (LCNEC) are poorly differentiated endocrine carcinoma. Histopathologically, they need to be differentiated from poorly differentiated adenocarcinoma in which immunohistochemistry is of help as the prognosis of LCNECs is significantly worse than that of conventional adenocarcinomas. As NE carcinomas are frequently chemosensitive, accurate initial diagnosis of these patients is important.

CASE SUMMARY:
40 years old female presented with recurrent vomiting and pain abdomen which increased after intake of food and relieved by vomiting, loss of weight and appetite of two months duration.

Keyword: Carcinoid tumor, Neuroendocrine carcinoma, Stomach, Chromogranin, Neuron specific enolase.
On examination, the patient was severely anemic, with tender epigastric mass. A provisional clinical diagnosis of Gastric carcinoma was made. On endoscopy, an ulceroproliferative growth involving mid-body extending upto antrum was seen and biopsy was taken and sent for histopathological examination. Histopathological examination showed the features of a poorly differentiated neoplasm. Subtotal gastrectomy was done and sent for histopathological examination which measured 17x7x5 cm with an ulcerated growth in the body of stomach measuring 8x7 cm. Cut section of the growth was grey-white with induration extending upto the distal margin. [Fig. 1]

Fig. 1 Subtotal gastrectomy specimen showing an ulcerative growth extending upto the distal margin. Microscopy revealed ulcerated mucosa, with a neoplasm in submucosa arranged in insular, trabecular pattern and in nests separated by fibrovascular septa. [Fig. 2 & Fig. 3].

Fig. 2 showed ulcerated mucosa with a neoplasm in submucosa (H&E, x100)

Fig. 3 Tumor cells arranged in insular pattern separated by fibrovascular septa (H&E, x400)

Cells were round with clear cytoplasm, round nuclei with clumped chromatin, 20 mitoses/10hpf with areas of necrosis with tumor infiltration into the muscle layer. [Fig. 4, Fig. 5, Fig. 6].
Fig. 4 Tumor cells infiltrating into muscle layer (H&E, x100)
Fig. 5 Tumor cells infiltrating into muscle layer (H&E, x100)

Fig. 6 Cells are round with clear cytoplasm, round nuclei with clumped chromatin with 20 mitoses/10 hpf (H&E,x400)

Fig. 7 Tumor cells showing positivity for Chromogranin(x100)

Fig. 8 Tumor cells showing positivity for Neuron Specific Enolase (x100)

Based on the histology, Large Cell Neuroendocrine Carcinoma- Grade 3 was made. Immunohistochemistry for Chromogranin [Fig. 7] & Neuron Specific Enolase. [Fig. 8] showed positive results.

**DISCUSSION:**

Neuroendocrine tumors (NET) can develop throughout the GIT but they are rare in oesophagus & anus (0.5%).[1] Most common site is small intestine (44.7%), followed by rectum (19.6%), appendix (16.7%) & colon (10.6%).[4]

Gastric NET arise from endocrine cells of the gastric mucosa, usually the Enterochromaffin like (ECL) cells. Gastric NET account for 11% to 41% of gastrointestinal neuroendocrine tumors [2] and are seen between 5th-6th decades of life.

Grossly, neuroendocrine tumors present as firm, grayish white, and fairly well circumscribed polyoid elevations of mucosa. [3] They acquire characteristic yellow color after formalin fixation. [3]

**WHO classification of neuroendocrine tumors of GIT**

Grade 1 neuroendocrine neoplasm-low grade <2mitoses/10hpf Grade 2 neuroendocrine neoplasm-high grade 2-10mitoses/10hpf Grade 3 neuroendocrine carcinoma- small cell & large cell >10 mitoses/10hpf

Histologically, NECs have a variety of histological patterns, including solid, organoid, trabecular, pseudo glandular, spindle cell, and rosette like. Based on both cell size and morphologic features, NECs are subdivided into two variants, namely, small cell NEC and large cell NEC. [6] Majority of gastric carcinoids are argyrophilic & react with the

PROGNOSIS:
The histologic features alone do not usually allow one to predict malignancy. The distinction between a benign and a malignant tumor is relied on the presence or absence of metastases. However, an elevated mitotic rate, and when the tumor invades beyond the submucosa, the tumor is considered to be potentially aggressive and has a worse prognosis.

5-year survival rate of grade 1 neuroendocrine tumors vary depending upon the site – appendix-86%, small intestine-59%, gastric-64% & colonic tumors-42%. Median survival rate of large cell neuroendocrine carcinoma is 8 months.

Neuroendocrine carcinoma needs to be differentiated from Neuroendocrine cell hyperplasia, Poorly differentiated adenocarcinoma, high-grade Non-Hodgkin Lymphoma (NHL) and epitheloid Gastrointestinal Stromal Tumor (GIST).

Neuroendocrine cell hyperplasia is a non-neoplastic proliferation of neuroendocrine cells. Histologically, it shows >5 coalescing nodules and each nodule with >5 endocrine cells in glands/crypts that do not exceed the diameter of gastric glands.

Differentiation of neuroendocrine carcinoma from poorly differentiated adenocarcinoma needs careful study of histological findings as the prognosis of large cell neuroendocrine carcinoma is significantly worse than adenocarcinoma. Nuclear features and absence of glands help to differentiate the two. Sometimes adenocarcinoma with neuroendocrine differentiation can co-exist. Hence extensive sampling is needed to look for glandular elements. Immunohistochemically, adenocarcinoma is positive for Cytokeratin and negative for neuroendocrine markers. 5-year survival rate of adenocarcinoma is 30%

A high-grade NHL shows sheet of pleomorphic & mitotically active blast cells with areas of necrosis. Immunohistochemistry is positive for CD 45, B/T cell markers helps to differentiate them from neuroendocrine carcinoma. 5-year survival rate of high grade lymphoma is 79-91%

Epitheloid Gastrointestinal stromal tumors (GIST) also present as submucosal lesion which can create problem. Histologically it show sheets or nests of cells with eosinophilic to clear cytoplasm, round to ovoid nuclei with finely dispersed chromatin & prominent nucleoli. Immunohistochemistry is positive for CD117, CD34. 5-year survival rate for low risk cases if 64% and for high risk cases is 35%

CONCLUSION:
Here a case of Large cell Neuroendocrine carcinoma of stomach is reported to stress on the need for accurate histopathological diagnosis as the treatment, behaviour, and prognosis is different from other tumors of GIT.

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