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Review Article

Neuroendocrine Carcinoma of Stomach: A Case Report and Review of Literature

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Abstract
Neuroendocrine neoplasms are rare tumors of stomach. In stomach these usually arise from enterochromaffin cells of Kulchitsky and can vary from benign to highly malignant tumors. These are divided into four distinct groups according to their clinicopathological behaviour. Type 1 are usually benign, are associated with chronic atrophic gastritis and carry a good prognosis. Type 2 are similar to type 1 in clinical presentation but metastatise in around 10-30% patients. Type 3 are sporadic, usually more than 2cm in size and need radical surgery. Type 4 are poorly differentiated, highly malignant tumors and carry a very poor prognosis.
Here we present a case of type 3 neuroendocrine carcinoma of the stomach which was diagnosed postoperatively by histopathology and confirmed by immunohistochemistry. The patient underwent a total gastrectomy with splenectomy with distal pancreatectomy with roux en-y-oesophagojejunostomy. We present this case due to its rarity. Review of literature done to emphasise the types and treatment of these tumors.
Keywords: *Neuroendocrine neoplasms,clinicopathologic,immunohistochemistry.*

Introduction

Neuroendocrine neoplasms of the stomach are rare tumors that account for less than 1% of gastric tumors.[1] These tumors mostly arise from enetrochromaffin like cells of the stomach and are divided into four distinct groups according to their clinicopathological behaviour.[2] Type 1 are associated with chronic atrophic gastritis and comprise almost 70-80% of neuroendocrine tumors of the stomach.[3] Type 2 are histologically similar to type 1 and is associated with Zollinger Ellison syndrome and multiple endocrine neoplasia. [1,4] Type 3 are sporadic tumors which are not usually associated with other gastric conditions. Type 4 are uncommon, usually single, poorly differentiated tumors.[5]

Here we report a case of type 3 neuroendocrine carcinoma of the stomach who underwent radical surgery in the form of total gastrectomy with splenectomy with distal pancreatectomy with roux en- y-esophagojejunostomy. We report this case due to its rarity. Review of literature done to highlight the types and modalities of treatment for this disease.

Case Report

A 45 year male presented in surgery OPD with complaints of pain epigastrium for 5 months and with one episode of malaena 3 days back. Pain was mild in intensity, intermittent, colicky in nature and non radiating. There was no history of vomiting, hematemesis or jaundice. History of significant weight loss and decreased appetite was present. There were no comorbidities present and there was no history of anti tubercular drug intake. Vitals were stable. On per abdomen examination an intra abdominal, intra peritoneal lump of size 6cm X 8cm present in the left hypochondrium was palpated. The lump had smooth surface, was non tender and had restricted mobility on respiration. No ascites was present. Rest of the abdominal examination and other systems were within normal limits. Digital rectal examination was within normal limits. A differential diagnosis of Gastrointestinal stromal tumor of the stomach or malignant adenocarcinoma of the stomach was kept.

Routine investigations revealed Hb – 6.4 gm/dl, Total proteins – 4.9 gm/dl and Serum albumin 2.2 gm/dl. All other routine haematological investigations were within normal limits. Usg abdomen revealed a well defined solid mass of size 117mm X 86mm in epigastrium and left hypochondria region, origin not clear ?Fundus/greater curvature of stomach.

CECT Abdomen showed well defined exophytich-eterogenous mildly enhancing mass of size 110 X 106 x 83 mm seen to be arising from posterior wall of stomach displacing it anteriorly. The surrounding fat planes with other organs were maintained. No enlarged aortocaval or paraaortic lymph nodes seen. Possibility of Gastrointestinal stromal tumor (GIST) of the stomach was kept. (Fig 1)

Gastro-videoscopy showed extrinsic compression of stomach from gastroesophageal junction to midbody of stomach on greater curvature. Overlying mucosa was normal.

So with possibility of GIST stomach the patient was built up and taken up for surgery.

On opening abdomen a large 14cm X 10 cm mass arising from posterior wall of stomach was present. Tumor was invading into spleen and distal pancreas. So a total gastrectomy with splenectomy with distal pancreatectomy followed by an anterior, dependent, retrocolic roux en y esophagojejunostomy was done. Rest of the solid organs were normal. There was no ascites or liver metastasis.

Gross examination of the resected specimen revealed a large growth of size14X10X7.5cms arising from the posterior wall of stomach (Fig 2) with erosion of overlying mucosa measuring. Cut section showed grey white to grey brown friable areas of necrosis and haemorrhage.

Histopathological examination showed tumor cells having pleomorphic large nuclei with stippled to vesicular chromatin and variably prominent nucleoli. Multinucleated tumor cells, frequent mitotic figures, lymphovascular invasion and foci of necrosis were seen. Tumor was involving the serosa. Both resection margins and lymph nodes were free from tumor. Mitotic index was >20/10 HPF (Fig 3)

A histopathological diagnosis of large cell neuroendocrine carcinoma was made and immunohistochemistry (IHC) done for final diagnosis. IHC was positive for pancytokeratin (Fig 4), cytokeratin 7, 20 and patchy strongly positive for synaptophysin and chromogranin (Fig 5). Ki-67 index was 20-25%. So a final diagnosis of *Type 3* WHO grade 3 neuroendocrine carcinoma of *stomach* was made.

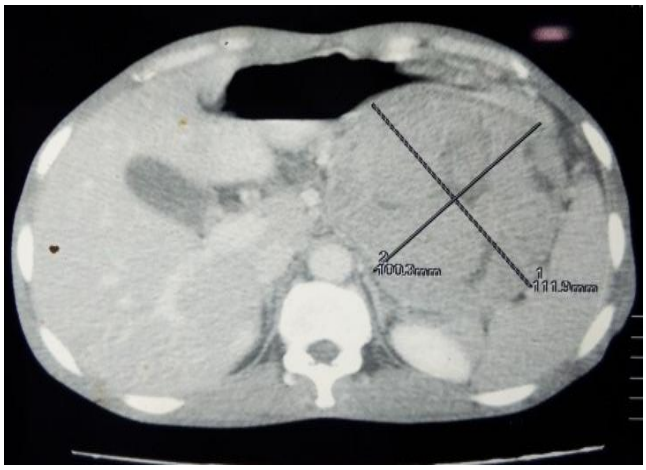

Fig 1: Cect abdomen of the patient showing a mass arising from posterior wall of stomach

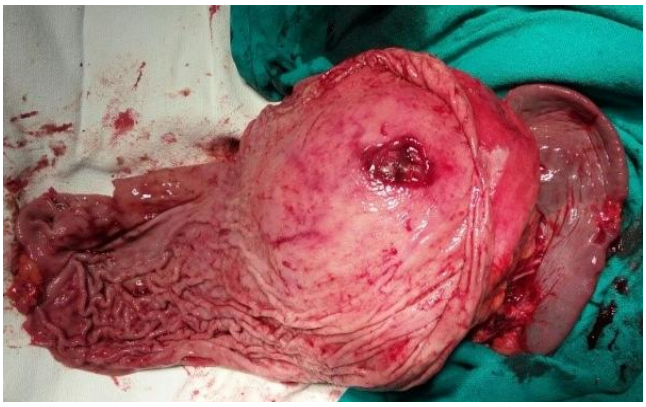

Fig 2: Resected specimen showing the growth

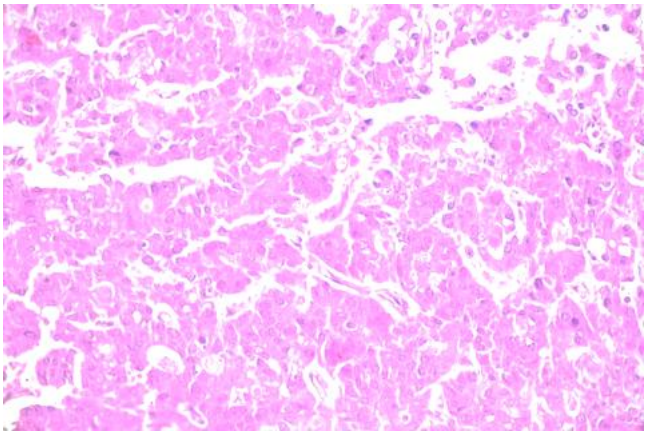

Fig 3: Histopathological photograph showing multinucleated tumor cells

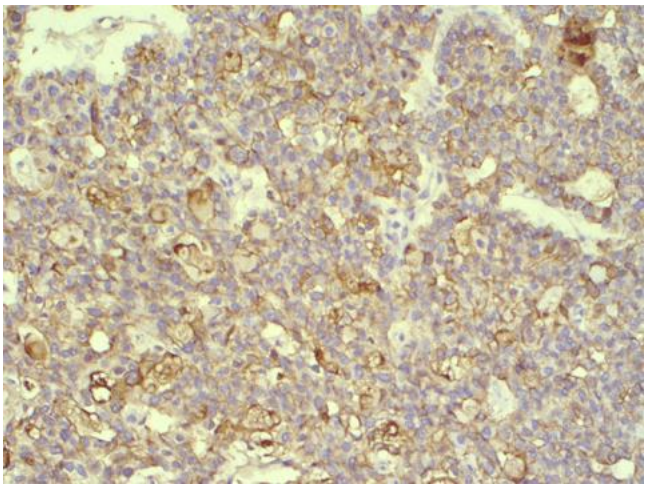

Fig 4: Immunohistochemistry image showing pancytokeratin positive

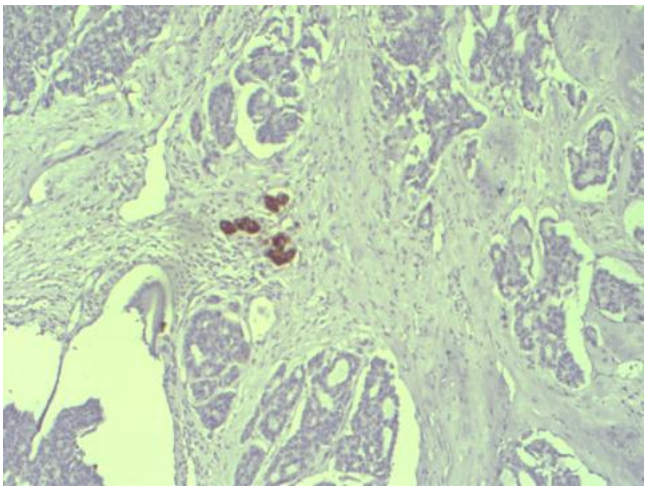

Fig 5: Immunohistochemistry image showing chromogranin patchy strongly positive

Discussion

Neuroendocrine neoplasia (NEN) comprise of epithelial neoplasia with neuroendocrine differentiation. The first reports of these tumors can be traced back to 19th century. Lubarsch in 1988 is credited with first report of such tumors from his work on autopsy materials.[6] In 1990, Ranson described a patient with a tumor of the terminal ileum, hepatic metastases, diarrhea and postprandial exacerbation of dyspnoea.[7] In 1907, Oberndorfer coined the term "carcinoid" (Karzinoid) to distinguish these tumors from the more common adeno carcinomas.[8] In GIT, these tumors may arise in appendix, small bowel, rectum, caecum, stomach and rarely even in pancreas, esophagus and liver. Ileum is the most

common site of NEN followed by rectum and appendix.

Gastric neuroendocrine neoplasms(GNEN) are rare tumors occurring in 1 to 2 cases/10^6 persons per year, and accounting for 8.7% of all gastrointestinal neuroendocrine tumors.[9] These were first described in 1923 by Askanazy.[10] Christodoulopoulos and Klotz reported 79 cases of carcinoid tumor of stomach mainly diagnosed at autopsy.[11]

Mean age of occurrence of Gastric NENs is around 64 years.[9,12] These tumors have a predilection for females and are rare in children. These are likely located in the fundus and body of the stomach, but can be derived from any location of the stomach.[13] These arise from the enterochromaffin cells of Kulchitsky i.e. neural crest cells situated at the base of crypts of Lieberkuhn.

These neoplasms can be either well differentiated neuroendocrine tumors (NET) or poorly differentiated neuroendocrine carcinomas (NEC). Most of these neoplasms are NETs and usually have an indolent course and carry a good prognosis.[9] NECs represent less than 10% of NENs and are difficult to diagnose preoperatively. Our case was a case of NEC diagnosed post operatively only after immunohistochemistry.

Gastric NEN's have been variously classified.The common classification systems used are one by American Joint Cancer Committee(AJCC)in 2009 and WHO in 2010. AJCC classifies GNEN on the basis of tumourinvasion, lymph node involvement and distant metastasis (TNM). According to WHO there are four groups of NENs in the stomach on thebasisof number of mitotic cells, proliferative, prognosis and biological behaviour.

Type 1 GNET are related to chronic atrophic gastritis and form majority of gastric NETs (70-80%). [13]These are multiple, usually less than 10mm and are located in fundus and body of stomach. In a study La Rosa et al reported 77% GNET Type 1 to be less than 10mm and 97% of less than 15mm.[12]It is very rarely metastatic with <5 % metastasis into lymph nodes and <2%distant spread and have a reported five yearsurvival of 100%.[14] Tumors in this group usually do not extend beyond mucosa or submucosa. Mitosis is rarely seen in these.KI-67 is usually less than 2%. Positivity for endocrine markers like chromog-ranin A (CgA) , neuron specific enolase, vesicular monoamine transporter 2 is increased.As this group of tumors is associated with good prognosis early diagnosis should be made. Endoscopy helps in suspicion and biopsy confirmation of these tumors. CT scan and endoscopic ultrasound help in evaluating depth of tumour. Endoscopic tumor resection is the treatment of choice for type 1 gastric NETs.[15]If multifocal GNET 1 (>4-6) or recurrent then gastric resection is required.[16]It has been reported that Netazepide, a highly selective, cholecystokinin 2 receptor antagonist of benzodiazipine class results in regression of tumor and normalisation of serum chromogranin.[17]

Type 2 GNET comprise 5-6% of gastric NETs and are associated *with* zollingerellison syndrome and multiple endocrine neoplasia. They are similar to type 1 in clinical presentation and are small, multiple and well differentiated tumors. These are also limited to mucosa and submucosa and metastasis in only around 10-30% cases.[18] Tumor related mortality is seen in <5 % cases. Mitotic count is <1 per 2HPF are seen in this group. KI-67 is expressed in less than 2% of tumor cells. Other than CT scan and endoscopic ultrasono-graphy, somatostatin receptor scintigraphy may help in diagnosing type 2 tumors. Due to presence of multiple tumors somatostatin analogues play a great role in treatment of type 2 tumors. These along with endoscopic resection are the treatment of choice for type 2 tumors.[19]

Type 3GNET tumors are sporadic and comprise 15-20% of gastric NETs. [20]These are usually more than 2cm in size, solitary, are non gastrin dependent, and grow from gastric body and fundus with normal surrounding mucosa. This type is aggressive and is usually associated with metastasis. Mitosis more than 1 per HPF is seen. more than 2% of tumor cells express the proliferation marker KI-67 but are negative for

CgA.[21]These carry a poor prognosis. Tumor related mortality is 25-87%. Radical surgery along with regional lymphadenectomy is the treatment of choice for this type.[22]Our patient was a type 3 gastric NET and underwent radical surgery along with post operative chemotherapy.

Type 4 GNET is rare, large and poorly differentiated tumor.[21] Unlike the first three types which are derived from enterochromaffin like cells, type 4 consists of other types of endocrine cell tumors (that secrete serotonin, gastrin, or adrenocorticotrophic hormone) and mixed endocrine-exocrine tumors. It usually shows angio andlymphoinvasion at the time of diagnosis. These frequently show atypical mitosis and KI- 67 index is more than 30. CgAis usually negative in these tumors. Radical surgery along with multi drug chemotherapy is the treatment for this group of tumors.[23] Mean survival time is 6.5 to 14.9 months.[20]

For staging of these tumors TNM classification is used. [16]

Table 1: TNM classification of gastric neuroendocrine neoplasm

Primary tumor (T)	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ/dysplasia (tumor size less than 0.5mm), confined to mucosa
T1	Tumor invades lamina propria or submucosa and 1cm or less in size
T2	Tumor invades muscularispropria or more than 1cm in size
T3	Tumor penetrates subserosa
T4	Tumor invades visceral peritoneum or other organs or adjacent structures
Regional lymph nodes (N)	
Nx	Cannot be assessed
N0	No Regional lymph node metastasis
N1	Regional lymph node metastasis
Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis present

According to TNM classification our patient was T4N0M0

The WHO 2010 classification divides NETs into : Low-grade (G1) tumors show a Ki-67 index less than 2%, or mitotic activity of fewer than 2 per 10 HPFs. Intermediate grade (G2) tumors have a Ki-67 index from 3% to 30% or mitotic activity of 2 to 20 per HPF and grade 3 high grade neuroendocrine carcinomas have a Ki-67 greater than 20% or mitotic rate greater than 20 per HPF.[24]

Mitotic rate should be based upon counting 50 high-power (40x objective) fields in the area of highest mitotic activity and reported as number of mitoses per 10 HPF. The mitotic index should be calculated by counting at least 500 and preferably 2000 cells

Ki-67 index is reported as percent positive tumor cells in area of highest nuclear labeling although the precise method of assessment has not been standardized. It has been recommended that 500 to 2000 tumor cells be counted to determine the Ki-67 index.[25]

Grade assigned based on Ki-67 index may be higher than that based on mitotic count. Thus, reporting the higher grade by either method is preferred if both are performed.

Table 2: Relation of grade with metastasis

Grade	Approximate incidence of node metastasis	Approximate incidence of distant metastasis
G1	5%	2.5%
G2	30%	10%
G3	70%	70%

For follow up of type 1 and type 2 tumors endoscopies are recommended every 6 to 12 months till 3 years and annually thereafter. Type 3 should be reevaluated 3 to 12 months' after resection and then every 6 to 12 months upto 10 years.[16]

Conclusion

Although a rare tumor, neuroendocrine carcinoma should be considered as one of the differential diagnosis in masses arising from stomach. An early diagnosis and appropriate treatment can be instituted before lymphatic spread and dissemination is supervened.

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