ISSN: 0975-833X

Available online at http://www.journalcra.com

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

International Journal of Current Research
Vol. 14, Issue, 03, pp.21134-21138, March, 2022

DOI: https://doi.org/10.24941/ijcr.43313.03.2022

RESEARCH ARTICLE

A RARE CASE OF ENDOSCOPICALLY MANAGED TYPE III GNET

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ARTICLE INFO

Article History:
Received 24th December, 2021
Received in revised form
19th January, 2022
Accepted 24th February, 2022
Published online 30th March, 2022

Keywords:

Gastric neuroendocrine tumor type III, Gastroenteropancreatic Neuroendocrine tumors, Gastric polyp, Neuroendocrine tumors, gastric Neuroendocrine tumors.

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ABSTRACT

Gastric neuroendocrine tumor (GNET) is a part of the more heterogenousGastroenteropancreatic - Neuroendocrine tumors (GEP-NET). A rare case of type III GNET is reported in this article. A 44 year old male presented with dyspepsia symptoms and on upper gastrointestinal (UGI) endoscopy he was incidentally identified with a solitary polyp in the body of the stomach. The histopathological examination of the biopsy was reported as Gastric neuroendocrine tumor (GNET). He was evaluated completely as per the recent consensus available and was managed successfully. The recent times explosion in the incidence of the neuroendocrine tumors and the complexity they pose in their management made obligatory to report this case.

Citation: Balasubramanian Arumugam, Madhusudhan Napa, Prabhakar, R., Bhanumati Giridharan, Shanmugasundaram, P.N. and Meenakshisundaram, K. *"*A rare case of endoscopically managed type iii gnet", *2022. International Journal of Current Research, 14, (03), 21134-21138.*

INTRODUCTION

Gastric neuroendocrine tumors (GNET) are recently being diagnosed in more numbers due to the increased availability and performance of upper gastrointestinal endoscopies (1).

Based on the clinical course, the Gastric neuroendocrine tumors are classified into four different types (1). Of these, Gastric neuroendocrine tumor type III has the potential to spread quickly and is typically diagnosed as a metastatic disease in about 50% of cases (1). Considering the early tendency to metastasize even at a size of 1 cm, radical surgery with regional lymph nodal clearance forms the

optimum treatment for the incidentally detected non-metastatic lesions. As opposed to their aggressive nature, type III gastroendocrinetumors typically present as solitary polyps measuring between 1-2 cm in the body of the stomach, which are suitable for endoscopic treatment. A successful endoscopic removal of the tumor in a non-metastatic type III GNET will be very beneficial to the affected patients. This subset of tumors should be carefully selected depending on the size and metastatic workup. It is vital to understand the feasibility and prerequisites of the endoscopic removal options for a successful outcome. This article will enlighten one such case of endoscopically managed typeIII GNET.

CASE REPORT

A 44 year old male with no comorbidities was evaluated for dyspeptic symptoms by UGI endoscopy way back in 2019. Incidentally he was detected with a subcentimetric (5 x 5 mm) sessile solitary polyp in the body of the stomach along the greater curvature (Figure 1). Multiple endoscopic biopsies were taken both from the polyp and from the other areas of the stomach. The histopathological examination (HPE) of the polyp was reported as well differentiated grade-I (G1) neuroendocrine tumor, characterized by cords and nests of tumorcells with salt and pepper nuclear chromatin (Figure 2 & 3). The immune histochemical markers (chromogranin and S-100 positive) confirmed the neuroendocrine origin (Figure 4). The biopsy taken from the other areas of stomach showed features of atrophic gastritis. He had then lost follow up and presented a year later.

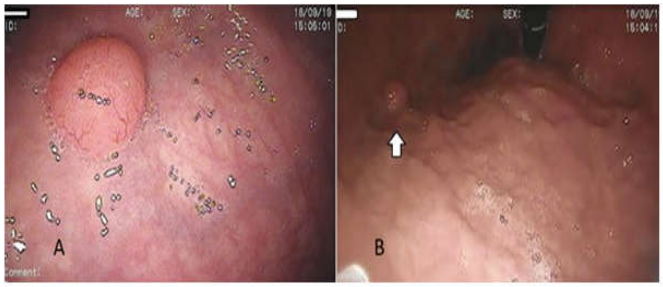

Figure 1. Endoscopic view of the sessile 5 x 5 mm polyp (A) located along the greater curvature in the body of the stomach (B)

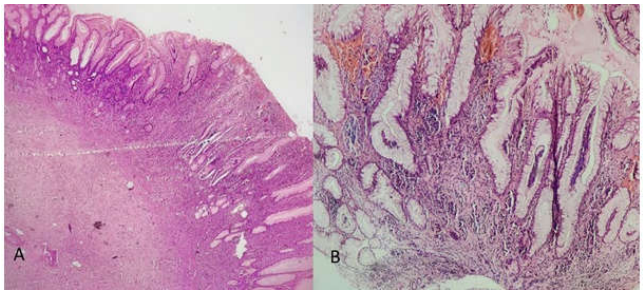

Figure 2. Histopathology. Low power (A) and High power (B) views of the section from the polyp

The repeat endoscopy showed the similar findings with no progression. He was then evaluated as per the recent available protocols of GNET. Serum chromogranin A was done to confirm the neuroendocrine origin and to have an index value for follow-up. He had an elevated serum chromogranin A levels confirming the neuroendocrine origin (1366.07 ng/ml {Normal :< 108}) His serum gastrin levels were done after a two week period of abstinence from proton pump inhibitors, which were within normal limits (67pg/ml). The normal gastrin levels ruled out the possibility of gastrin dependent Type I &II of GNET. Subsequently a Contrast enhanced Computer tomography (CECT) of abdomen was performed, which identified the localised polyp with no features of metastasis (Figure 5). According to the results of the initial diagnostic investigations, it was a single sessile subcentimetric type III GNET without evidence of metastasis. The in-house tumour board called for an expert Medical gastroenterology centre opinion for the feasibility of endoscopic excision considering the localized disease and lower mitotic ki-67 index of 2 (Figure 4). Subsequently a whole body somatostatin receptor imaging with Ga68- DOTANOC PET CT scan was done for the patient which showed mild increased uptake at the polyp with no other uptake elsewhere (Figure 6). The patient underwent an endoscopic snare polypectomy and the specimen was 0.7x0.6x0.5 cm in size. The histopathological examination showed no invasion of tumor cells beyond the mucosa and the margins were free of tumor cells. The patient is on regular follow-up with UGI scopy for past one year and is disease free.

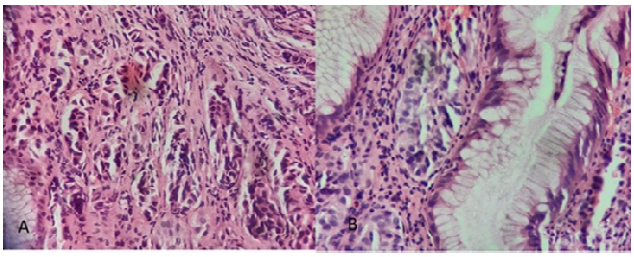

Figure 3. Histopathology demonstrating cords and nests of tumor cells with round nucleus and salt & Pepper Nuclear Chromatin

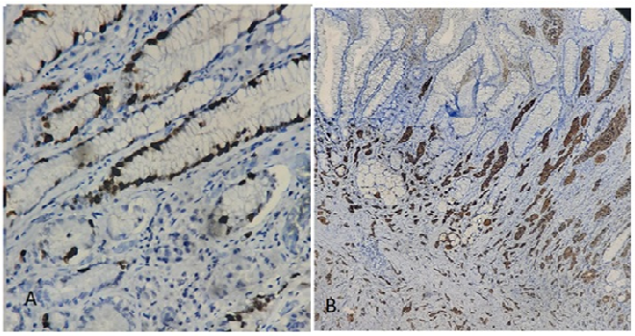

Figure 4. Immunohistochemistry showing ki67 (A) and chromogranin (B) positive staining.

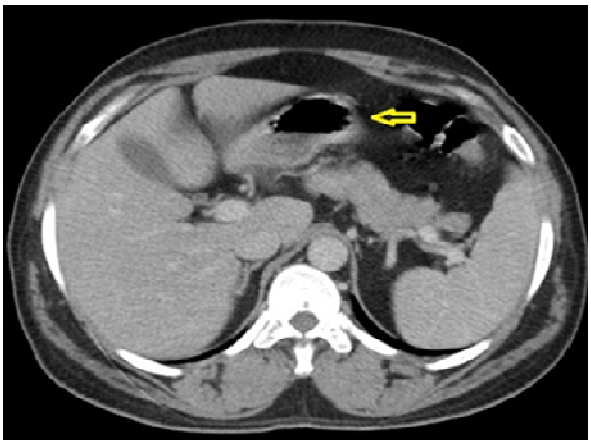

Figure 5. Computed tomography of abdomen (axial cuts) showing a subcentimetric polyp in greater curvature of stomach (yellow arrow)

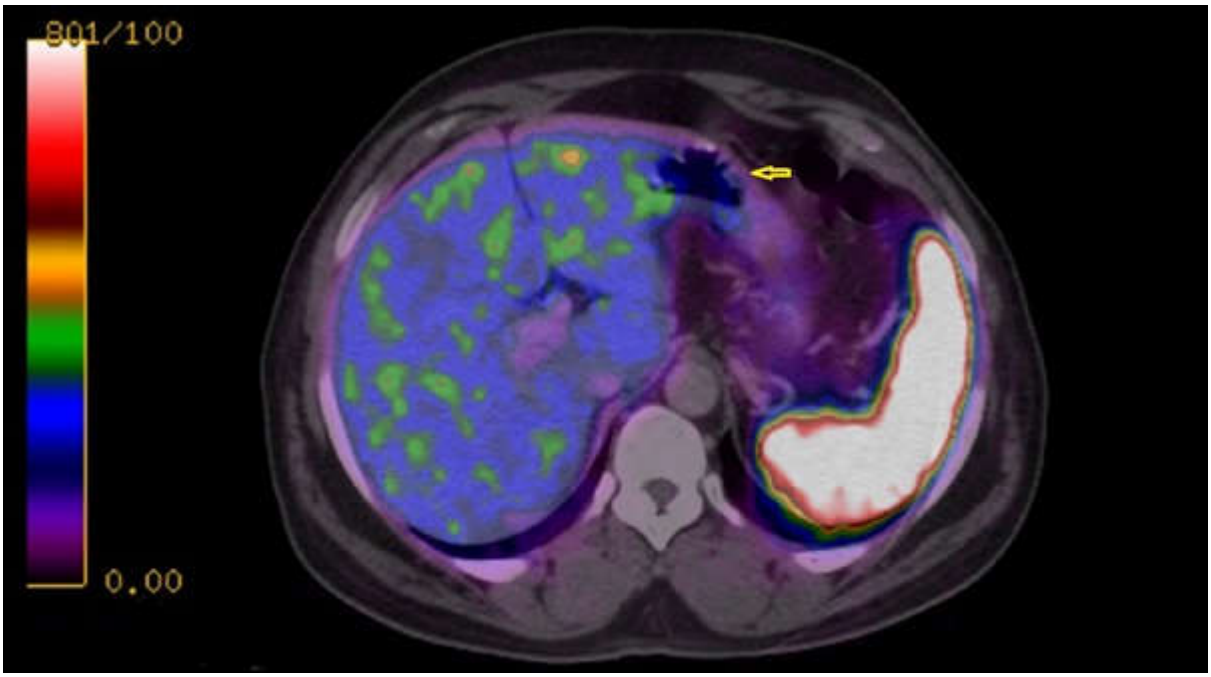

Figure 6. Whole body somatostatin receptor imaging with Ga68- DOTANOC PET CT showing mild increased uptake at the polyp (yellow arrow)

Table1. Who classification of gastrointestinal neuroendocrine neoplasm(nen),2017(4th edition)

A.WELL DIFFERENTIATED NEUROENDOCRINE NEOPLASMS (NET)		
	Mitotic index/2mm^2	Ki67 index
NET grade 1	<2	<3
NET grade 2	2-20	3-20
NET grade3	>20	>20
B. POORLY DIFFERENTIATED NEUROENDOCRINE NEOPLASMS(NEC)		
NEC grade3 - Small cell type - Large cell type	>20	>20
Mixed Neuroendocrine Neoplasms (MiNEN)	Each component must be at least 30% to fall into the category of MiNEN	
5th Edition of WHO classification-2019, has included that mutations in MEN1, DAXX and ATRX are entity-defining for well-differentiated NETs, while NECs usually have *TP53* or *RB1* mutations		

Table 2. Classification of gnets

PRESENTATIONS	TYPEI	TYPE II	TYPE III	TYPE IV
Occurrence	70-80%	5-6%	15-20%	Very rare
Cell of origin	ECL	ECL	ECL	Non-ECL
Location	Body & Fundus	Body & Fundus	Anywhere	anywhere
Gastrin dependency	Increased serum Gastrin with background of atrophic gastritis	Increased serum Gastrin due to Gastrinoma	Normogastrinemia	Not gastrin dependent but may be increased in 1/3rd cases
Endoscopic presentation	Multiple subcentimeter polyps	Multiple small polyps	Solitary polyp usually> 2cm	Single large > 4cm polyp
Proliferation index Ki67	<2%	<2%	>2%	>30%
Risk of metastasis	2-5%	10-30%	50-100%	100%

DISCUSSION

Neuroendocrine tumors are neoplasms developing from specialized cells of body, which has both neural (dense core granules in cytoplasm similar to serotonergic neurons) and endocrine (can synthesize monoamines) elements in them and are ubiquitous. A larger proportion of them occur in Gastrointestinal tract (about 55%), which were earlier named distinctly depending upon their origin area as APUDomas, carcinoids or islet cell tumor (1).

The broad nomenclature of Gastroenteropancreatic-neuroendocrine tumors (GEP- NET) has been recently used to avoid confusion to include all gastrointestinal NETs though heterogeneity still exists. The incidence rate has steadily increased of about more than 400% over the last 40 years and data is showing an increasing afflicted rate from 1 per 100,000 to 5 per 100,000 populations (2). GEP-NET contributes to about 2% of all Gastrointestinal malignancies (1). GEP-NET are becoming more common than many of the gastrointestinal tumors and are affecting the younger age population, when compared to other types of tumors.

They can occur either commonly as sporadic or associated with hereditary diseases such as multiple endocrine neoplasia type 1, Von Hippel-Lindau's disease or neurofibromatosis type 1. Most of the GEP-NETs are non-functional, making them difficult to diagnose at an initial stage and if functional, they classically present with clinical syndromes such as carcinoid, zollinger -ellison and so on. The most commonly used tumor marker has been serum chromogranin A for both functional and non-functional tumors and is increased in 80-90% cases. The serum chromogranin A is used as diagnostic, prognostic and also as a follow -up tool. The 24 hrs urinary 5-hydroxyimino acetic acid (5-HIAA) can also be used as a marker to identify only serotonin secreting (functional) tumors.

The WHO classification of neuroendocrine tumors has evolved over the years. The 2017 classification is based on histological grading which includes cellular differentiation, mitotic index and Ki67 expression (Table 1). The neuroendocrine neoplasms (NEN) has been broadly classified as well differentiated Neuroendocrine tumors (NET) and poorly differentiated Neuroendocrine carcinomas (NEC) and the grade3 NET has been now separately classified because of better prognosis than neuroendocrine carcinoma (NEC)grade3 (3,4). Gastric Neuroendocrine tumors (GNET) contributes to about 7-8% of all NETs (5). Most of them develop from Enterochromaffin-like cells (ECL). As per incidence GNETs have recorded a tenfold increase in last 40 years. The increase may be due to extensive use of UGI endoscopies, better immunohistochemical staining facilities and overall increased awareness. Apart from the WHO classification, GNETs have been classified into four clinical types based on their clinical course, biology and prognosis (Table 2). In fact the later one is more widely practised. The hypergastrinemia, either due to atrophic gastritis (Type I) or gastrin secreting tumors (Type II) has been the underlying cause in first two types. Also the hypergastrinemia stimulates multiple polyps formation. Type I & II behave almost alike except for their cause of hypergastrinemia and carry lesser risk of metastasis favouring them for the options of endoscopic removal and surveillance. The Type IV is an eccentric type with the most aggressive behaviour, almost always presenting with distant blood borne metastasis and high mitotic index. The Type III is next common to type I and usually presents with solitary polyp of > 2 cm and has normal gastrin levels. They can be both well differentiated (25%) and poorly differentiated (75%) with mitosis rate of >1 per HPF.

The Ki67 index is usually > 2 %. They are prone of lymph nodal and hepatic metastasis and nearly 50% tumors present with metastasis at the time of diagnosis (7). The overall 5 year survival rate ranges from 25-75% depending on their histological differentiation (6). The high risk features favour the initial surgical resection whenever possible. Only in few selected cases with smaller lesions (<1cm), well differentiated histopathology, low Ki67 index and absence of invasion beyond submucosa, Endoscopic removal is done (7). Endoscopic procedures include simple snare polypectomy, Endoscopic Mucosal resection (EMR) and Endoscopic submucosal dissection (ESD). The size and the depth of tumor are deciding factors in the outcome of endoscopic treatment. In most cases where tumor is less than 1 cm EMR was good and enough. ESD can be reserved for >2cm polyp with submucosal disease. Yong Hwan Kwon et al (2013) has reported 80% complete pathological resection with endoscopic methods.

Intra-epithelial lesions and tumors involving only uptolaminapropria can be dealt with simple snare polypectomy in Type III GNET, provided their tumor biology is favourable. However post procedure these patients require a vigilant and frequent surveillance with follow-up endoscopies required at 3rd, 6th & 12th month post procedure to pick up the recurrence. Imaging and serum markers are also to be done and followed up. Patient needs to follow up for a period of 10 years. Any recurrence needs surgical resections ranging from wedge resections to distal gastrectomy or total gastrectomy with regional lymphadenectomy. The management options for metastatic lesions have also sprung up in large numbers and include octreotide therapy(for carcinoid syndrome), systemic chemotherapy (streptozocin, 5-fluorouracil with leucovorin, cyclophosphamide, doxorubicin, oxaplatin, dacarbazine), molecular targeted agents (bevacizumab, sunitinib, sorafenib, everolimus), targeted peptide receptor radionucleotide therapies (PRRT) (indium-DTPA-octreotide, Lutetium-DOTA-Tyr3-octreotide, Yttrium-DOTA-Tyr3-octreotide), transarterial chemoembolization (TACE) and radiofrequency ablation (for symptomatic hepatic metastasis).

CONCLUSION

With the increasing trends of GNETs and their more varied presentations, treatment decision should be tailored made according to the latest available consensus and guidelines. In TypeIII GNETs, surgical resection will be the standard treatment due to their metastatic potential, however, endoscopic resection can benefit a subset of carefully selected patients, avoiding the morbidities of surgery.

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