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Original Article

Clinicopathologic profile of gastroenteropancreatic neuroendocrine neoplasms in a referral center of South India

Temjen Sunup Jamir[1], Bhawana Ashok Badhe[2], Norton Stephen[3], Bheemanathi Hanuman Srinivas[4], Biju Pottakkat[5]

[1]North Eastern Indira Gandhi Regional Institute of Health and Medical Sciences, Shillong, Meghalaya, India; [2]Department of Pathology, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry, India; [3]Department of Pathology, Sri Venkateshwara Medical College, Hospital and Research Centre [SVMCH&RC], Puducherry, India; [4]Department of Pathology, JIPMER, Puducherry, India; [5]Department of Surgical Gastroenterology, JIPMER, Puducherry, India

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Abstract: Background: The neuroendocrine system of the gastroenteropancreatic (GEP) region gives rise to unique, heterogeneous malignancies that need a high index of suspicion to make a diagnosis owing to their indolent course. Aims: The present study aimed to find the incidence and the differences in the morphologic and immunohistochemical profile of gastroenteropancreatic neuroendocrine tumors (GEPNET) in a referral center of South India, JIPMER, Puducherry, India. Methods: There were 55 gastroenteropancreatic region neuroendocrine neoplasms (NEN) assessed for demographic, clinical and radiological features. Gross morphological features, histopathological features, mitotic index, Ki67 proliferation index, and immunohistochemical positivity for synaptophysin, chromogranin-A, CD-56, NSE (Neuron Specific Enolase) and pan-cytokeratin (Pan-CK) were also assessed. Results: The majority were nonfunctional tumors presenting with abdominal pain, gastrointestinal bleed, vomiting, jaundice, and loss of weight and appetite. The sites of involvement according to the order of frequency were duodenum, stomach, rectum, pancreas, ileum, appendix and jejunum. The endoscopic appearance of duodenal and jejunal tumors showed polypoidal, nodular and ulceroproliferative growth. These tumors were diagnosed by preoperative biopsy; 54% of them were grade-1 neuroendocrine tumors exhibiting nesting, trabecular, cord, and solid sheet patterns. All 55 cases were synaptophysin-positive with variable positivity for chromogranin, neuron-specific enolase, CD56, and Pan-CK. Mixed adenoneuroendocrine carcinomas (MANECs) involving the duodenum and stomach comprised 7.3% of all GEPNETs. Pancreatic neuroendocrine tumors constituted 9% of all tumors; one was multifocal. Lymph node metastasis was seen in 12/55 tumors; 6/12 showed liver metastasis also. All metastasizing tumors measured less than 4 cm in size. Statistical correlation of the tumor grade, mitotic count and Ki67 index as analysed by Spearman's correlation between the paired data denoted by r^s in 55 tumors showed a strong correlation between mitotic count and Ki67 index; a moderate correlation was noted between the tumor grade and Ki67 index. Conclusion: The clinicopathologic profile of 55 GEPNET revealed a majority to be sporadic Grade 1 tumor. Tumors that showed lymph node and liver metastasis were less than 4 cm in size. MANECs were found in the duodenum and stomach.

Keywords: Gastroenteropancreatic neuroendocrine tumors, mixed neuroendocrine-non-neuroendocrine neoplasms, immunohistochemistry

Introduction

Gastroenteropancreatic neuroendocrine tumors are heterogeneous malignancies arising from the diffuse neuroendocrine system with unique features and a generally indolent clinical course. It is difficult to predict their prognosis. The prognosis is affected by age, gender, disease stage and urinary 5 hydroxy-indole acetic acid levels. The presence of carcinoid heart disease further influences patient survival [1, 2]. Irrespective of the site of origin, the histology is similar [3] with distinct functional and biological behavior depending on location, tumor size, and clinical symptoms [6].

Gastroenteropancreatic tumors are rare, accounting for 2.5 to 5 cases/100,000 popula-

tion [4]. Based on SEER data, the incidence rates of GEPNET and all gastrointestinal cancers were determined to equal 3.5 and 62.1, respectively per 100,000 per year from 2000 through 2014 [5]. NET represents 5.84% of all newly diagnosed GEP cancers [5].

The cells that give rise to GEPNET derive from gastrointestinal stem cells that can differentiate into neuroendocrine cells that ultra-structurally show dense core secretory granules containing peptides and amines [6]. Presently they can be identified by immunohistochemically staining for secretory granules and their products, namely chromogranin-A, synaptophysin, neuron-specific enolase, and CD56, and being epithelial, also express cytokeratin to varying degrees [7-9].

These tumors are classified according to the 2010 WHO classification by introducing neuroendocrine neoplasms (NEN) as a term to encompass these tumors, with the grading of tumors based on a proliferative fraction, using mitotic count (MI) and Ki67 index. The grade 1 tumors (G1) exhibit MI <2/10 HPF and Ki67 index of <3% while grade 2 tumors (G2) exhibit MI 2-20/10 HPF and Ki67 index of 3-20%, and grade 3 tumors (G3) exhibit MI >20/10 HPF and Ki67 index of >20%, and certain grade 3 tumors are further referred to as neuroendocrine carcinomas (NEC) of either small cell or large cell type based on their differentiation and morphology [10, 11]. E.g., some pancreatic NET, found to have well differentiated histology but having Ki67 index >20%, are categorized as Pan NET G3 (pancreatic neuroendocrine tumor grade 3).

The term mixed neuroendocrine-non-neuroendocrine neoplasm (MINEN) was added in the 2017 WHO classification of pancreatic tumors for mixed neoplasms that were previously called mixed adenoneuroendocrine carcinomas (MANECs) [12]. This classification includes well differentiated Pan NET-G1, G2, G3, and poorly differentiated NEN G3 and NEC small cell and large cell types [10].

Pancreatic NETs are usually malignant (exception: insulinoma), and Pan NETs have a worse prognosis compared to GEPNET at other sites [6]. The presence of liver metastasis is the single most important prognostic factor for GEPNETs [13-15]. The prognosis is also influenced by grade (G1-G3) and TNM classification, with higher stage and higher grade associated with a worse prognosis. The present study was conducted to study the frequency and the differences in the morphologic and immunohistochemical profile of gastroenteropancreatic neuroendocrine tumors in a referral center of South India, JIPMER, Puducherry.

Materials and methods

A cross-sectional descriptive study was conducted on gastroenteropancreatic neuroendocrine tumors presenting to the Department of Pathology, JIPMER, Puducherry from January 2011 to July 2018, that included retrospective patients from Jan. 2011 to October 2016 and prospective patients from November 2016 to July 2018. Approval from the postgraduate research monitoring committee (PGRMC) and the Institutional ethics committee (IEC) approval were obtained for the study. There were 55 Gastroenteropancreatic (GEP) region neuroendocrine neoplasms (NEN) diagnosed during the study period. They were assessed for demographic, clinical, and radiologic features, gross morphologic features, histopathologic features, mitotic index, Ki67 proliferation index and immunohistochemical positivity for neuroendocrine markers such as synaptophysin, chromogranin-A, CD-56, NSE, and pan-cytokeratin (Pan-CK).

The grading of NEN was carried out according to the 2010 WHO classification of neuroendocrine neoplasms of the gastrointestinal tract and the 2017 WHO classification of neoplasms of the neuroendocrine pancreas. The organ-specific TNM classification of NEN was used to stage these tumors.

Statistical analysis

Statistical analysis was carried out using IBM SPSS software version 19, and State version 14 was used for analyzing Spearman's correlation among tumor grade, mitotic activity, and Ki67 expression. The distribution of data in categorical variables such as gender, clinical characteristics and immunohistochemical profile were expressed as frequencies and percentages. The continuous data like age and tumor size were expressed as mean with standard deviation or median with interquartile range.

Table 1. Most common sites of origin of neuroendocrine tumors

	Bruna Estrozi *et al.* [21]	Amarapurkar DN *et al.* [20]	Nadler A *et al.* [22]	Megha S. Uppin *et al.* [7]	Maggard *et al.* [16]	Present study
Most common site	Stomach (24.5%)	Stomach (32.5%)	Small bowel (27%)	Duodenum and periampullary (22.5%)	Small intestine (44.7%)	Duodenum (31%)

Results

Case frequency

This study described the clinicopathologic profile of 55 patients of NEN in the GEP region. There were 9 patients for whom slides and blocks were not available for immunohistochemistry (IHC) as they had been issued to the patient for external referral at their request. The frequency of occurrence of GEPNET at our referral center (JIPMER, Puducherry) was 2.21% out of 2486 GEP malignancies during the study period of 7 years and 6 months from January 2011 to July 2018.

Demographic data

The age of patients ranged from 21-73 years with a mean age of 51.4 years; 87% of patients were between 30 and 70 years. An M: F ratio of 1.3:1 was noted.

Clinical features

Fifty-six (96%) patients had nonfunctional tumors and presented with complaints of abdominal pain, gastrointestinal bleed, vomiting, jaundice, loss of weight and loss of appetite. 6 of these patients were asymptomatic.

Two (4%) patients had functional tumors and presented with complaints of breathlessness, syncope, and disorientation.

Frequency by site

Of the 55 gastroenteropancreatic NET, the duodenum was the most common location (31%) for these lesions. The regional distribution of GEPNET showed involvement of the duodenum (31%), stomach (25%), rectum (24%), pancreas (9%), ileum (5%) appendix (4%) and jejunum (2%) (**Table 1**).

Endoscopic appearance

Endoscopy performed for 14 gastric and 12 duodenal tumors showed that gastric NENs were located in the body (5) and antrum (5) of the stomach, fundus (2), and pylorus (2) while duodenal tumors were seen in the D1 (6), D2 (5), and D3 (1) region.

Endoscopic examination revealed 8 polyps, 6 nodules, 6 ulceroproliferative, 5 ulcerative, and 1 proliferative growth pattern.

Histomorphology

Histomorphologic features where preoperative biopsies were available (41/55 cases) revealed 54% grade 1 NET, 17% Grade 2 NET, and 14% grade 3 NET.

In 24 cases, post-operative resection specimens were also studied. On evaluating preoperative biopsies, 7 discordant diagnoses were noted. These included inadequate material, mucosal hyperplasia, and nonspecific duodenitis in 4 cases, while 3 cases of MANECs were reported as adenocarcinoma, highlighting the importance of proper sampling.

Histopathologically, the majority (89%) of the tumors showed a nesting pattern (**Figure 1**); other patterns noted were trabacular (25%), sheets (20%), cords (14%), acinar/pseudoglandular (13%) and cribriform (2%) pattern.

All 55 GEPNET irrespective of their grade, were arranged most commonly in nests, trabeculae, cords and sheets. The cribriform and acinar patterns were uncommon.

Tumor grades

In our study Grade 1 (64%) and Grade 2 (18%) were the most common grades of GEPNET presenting to JIPMER. MANECs (7%) and Grade 3 (11%) GEPNETS were restricted to the stomach and duodenum (**Table 2**).

24/55 cases were resected specimens, which were available for study.

These specimens of GEPNET consisted of stomach (6/24), duodenum (5/24), jejunum

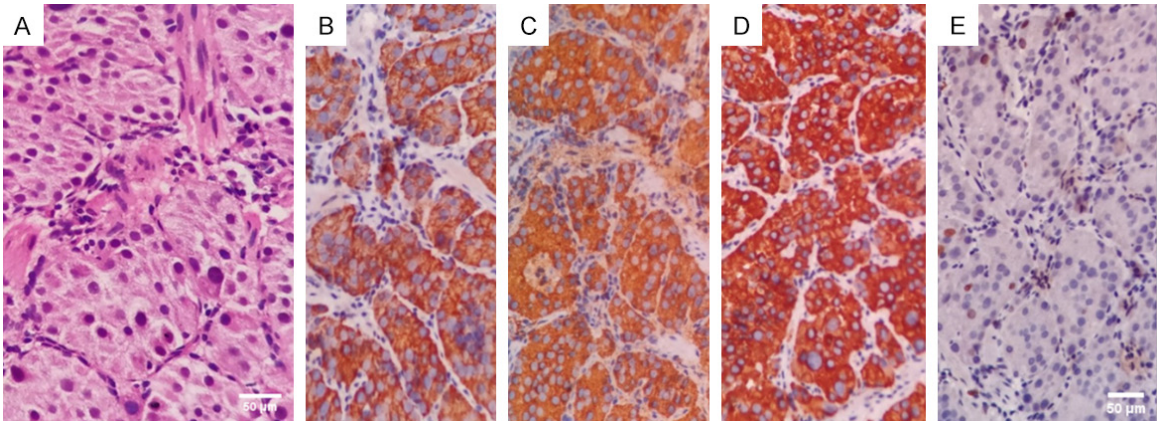

Figure 1. Grade-1 Gastric NET. A: Polygonal cells with nesting arrangement. These cells show abundant granular, eosinophilic cytoplasm. Nuclei show smudgy chromatin with inconspicuous nucleoli. B: Tumor cells are highlighted by synaptophysin. C: Chromogranin shows diffuse positivity in tumor cells. D: Pan-CK highlights the tumor cells. E: Ki67 index of 2% is noted (H&E ×400; IHC ×400).

Table 2. Frequency of grades of neuroendocrine tumors

Grade	BrunaEstrozi *et al.* [21]	Megha S. Uppin *et al.* [7]	Nadler A *et al.* [22]	Present Study
Grade 1	73.2%	48.3%	50%	64%
Grade 2	10.5%	31%	36%	18.2%
Grade 3	16.3%	17.2%	14%	11%
MANEC	-	3.5%	-	7.2%

(1/24), ileum (3/24), rectum (2/24), appendix (2/24) and pancreas (5/24).

Gastric NET included 3 cases of G1 and G2 NET combined, and 3 cases of MANECs. G1+G2 Gastric NET had an average size of 3.3 cm and the 3 MANECs had an average size of 6.3 cm. The average mitotic index was 4/10 HPF for G1+G2 Gastric NET, and 41.6/10 HPE for MANECs.

Concordantly the average Ki67 of G1+G2 Gastric NET and MANECS was 5% and 43.3%, respectively (**Figure 2**, **3**).

Duodenal NET included 3 cases of G1 and G2 NET combined, three G3, and one MANEC. The three G1&G2 NETs had an average size of 2.5 cm and an average mitotic count and Ki67 index of 1/10 HPF, and 1.3% respectively. The duodenal MANEC had a size of 1.8 cm, with mitoses of 5/10 HPF, and a 3% Ki67 index.

There were 5 cases of pancreatic NET ranging in size from 1-16 cm. These included 4 non-functional tumors with a mean size of 7 cm, and 1 functional tumor (insulinoma) that was multifocal, with the largest nodule measuring 1 cm. All the nonfunctional tumors were low grade (G1&G2) with one G2 tumor showing metastasis to the lymph node and the liver. The insulinoma was a grade 1 tumor and did not show metastasis.

Gross appearance

The comparison in size distribution between low grade (G1&G2) and high grade (G3&MANEC) tumors showed no significant difference in size.

The gross appearance of 24/55 resected gastroenteropancreatic neuroendocrine tumors revealed: polypoid 17%, proliferative 25%, ulcerative 9%, ulceroproliferative 6%, and nodular 43%, gross morphology.

Metastatic potential

The evaluation of metastatic status among 55 GEPNET revealed that 12 patients showed lymph node metastasis. 6 of these cases had liver metastasis in addition to lymph node metastasis. None of these tumors was greater than 4 cm in size. There was no case of distant

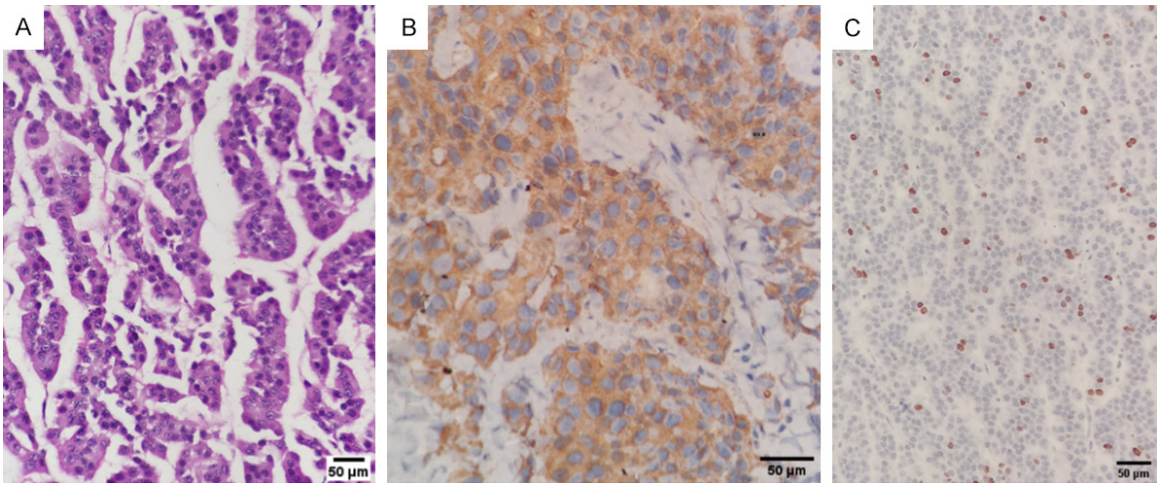

Figure 2. Case of G2 gastric neuroendocrine tumor. A: Tumor cells are arranged in nests, with the presence of irregularly distributed, stippled chromatin, and occasional conspicuous nucleoli. B: Chromogranin is positive in tumor cells. C: Ki67 index-14% (H&E-200×; Chromogranin-400×; Ki67-200×).

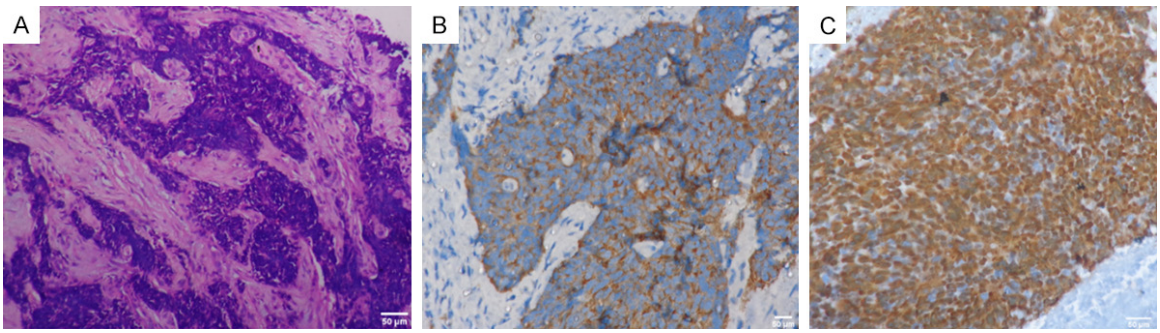

Figure 3. Case of gastric neuroendocrine carcinoma. A: Tumor cells are small, with stippled to hyperchromatic nuclear chromatin, and are arranged in solid sheets. B: Synaptophysin is positive in tumor cells. C: Ki67 index-100%. (H&E-200×; Synaptophysin-400×; Ki67-400×).

metastasis without LN involvement. The GEP-NETs were found to be metastasizing to the lymph nodes irrespective of the grade and size of the tumor. Duodenal, jejuno-ileal and rectal grade 1 and 2 GEPNET showed LN metastases. Ileo-jejunal and rectal tumors of grade 1 neuroendocrine tumor showed liver metastasis in addition to LN metastasis.

The gastric NET-despite being grade 3 and MANEC showed only nodal metastasis and did not show distant metastasis.

Immunohistochemistry

Immunohistochemical profile of GEPNET in 46/55 cases showed cytoplasmic synaptophysin expression by all the tumors. Chromogranin A was expressed in 89%, NSE by 74%, CD56 by 46%, and pan-CK by 80%. None of the pancreatic tumors showed CD56 positivity in our study.

The immunohistochemical expression of the above markers in these tumors, showed no significant correlation of expression with either site or grade.

Spearman's correlation coefficient measures the strength of correlation between paired data denoted by r^s. Correlation between tumor grade, mitotic count, and Ki67 index was analyzed for 55 GEPNET. Spearman's correlation analysis with mitotic count and Ki67 showed a strong correlation with an r^s value of 0.89.

The correlation coefficient between mitotic count and tumor grade was 0.62, while the correlation coefficient between tumor grade and Ki67 was 0.55, -both of which indicate a moderate correlation between the variables.

Discussion

The present study found 55 GEPNETs out of a total of 2486 malignancies of the gastroenteropancreatic region at our center during the study period. The SEER data from the 2000-2014 period reported the incidence rates of GEPNET and all gastroenteropancreatic malignancies per 100,000 per year to equal 3.5 and 62.1 respectively [5]. Thus 5.84% of all newly diagnosed GEP malignancies are NETs [5]. In our study, these tumors accounted for 2.21% of all malignancies in the gastroenteropancreatic region.

The age of most patients ranged from 30-70 years, with a mean age of 51.1 years, which is lower than most other studies which varied from 60.1 to 62 [7, 16, 18, 19]. There was also a slight male preponderance with a male: female ratio of 1.3:1, which is in concordance with the study by Amarapurkar et al. [20].

In concordance with the findings of Uppin et al., abdominal pain was the most common presenting symptom, and the duodenum (22.7%) was the most common site of gastroenteropancreatic neoplasms in our study [7]. The present study did not find any cecal or colonic NET. In the present study, tumors in the ileum, jejunum, and appendix were all grade 1 tumors. Grade 3 tumors and MANECs were located solely in the stomach and duodenum. Mixed adenoneuroendocrine carcinoma (7.3% of all cases), found in the duodenum and stomach in our study, is a neoplasm involving both epithelial and neuroendocrine components, with each component comprising at least 30% of the tumor, and both components being malignant.

All cases in the present study were sporadic and no syndromic association with MEN syndrome was identified. The nonfunctional tumors are more common than their functional counterpart and are indolent, and previously found to be larger and more frequently metastasizing at the time of diagnosis [23-25]. In our study, possibly due to increased health awareness, we found an overwhelming majority of nonfunctional tumors, with the majority of them being of low grade.

Nodal and distant metastases play an important role in prognosticating and managing these patients. The present study found 22% lymph node metastasis, with 11% showing distant metastasis. Yamaguchi et al. reported 7/45 cases showing metastasis, with 3/45 cases showing lymph node metastasis [26]. Uppin et al. reported 57% cases with nodal metastasis in 40 GEPNET studied which is significantly higher than our study [7]. Distant metastasis has been reported in previous studies to vary between 10.4 to 21%, which is similar to our study [18, 27-30].

In a previous study, 64% cases of pancreatic NET showed distant metastasis followed by 44%, 32%, and 30% of caecal, colonic and small intestinal NEN respectively [18]. In our study, of the 6 cases displaying distant metastasis, two cases were rectal NEN, followed by one each of duodenal, jejunal, ileal and pancreatic NEN.

The evaluation of the gross morphology of GEPNETs revealed a size range of 0.5-16 cm (mean size 1.8 cm). More than 5 cm sized tumors were gastric and pancreatic.

Microscopic patterns revealed nesting, cords, trabaculae, acini, cribriform and sheets of malignant cells. The high-grade tumors were predominantly arranged in sheets. This is in accordance with previous data [10].

As in previous studies, synaptophysin positivity was seen in all cases [7, 31, 32]. Chromogranin A was expressed by 89% of tumors overall. Rectal tumors in our study showed a 62% positive rate for chromogranin A, which is in concordance with a study by Wong et al., who found lower expression in hindgut NET compared to foregut and midgut tumors [33]. Other studies in the past have found chromogranin A positive rates of usually more than 83%, which is similar to our study [7, 31, 32].

In our study, the IHC marker with the least amount of positivity was CD56 (46%) with the highest positivity in the small intestine (55%) [7, 31, 34]. Our study showed a pan-CK positivity of 80%, while previous studies in the gastroenteropancreatic region have shown pan-CK positivity varying from 67% to 100% [7-9]. The NSE positivity in our study was 74% with varying degrees of positivity seen across different organs. Terada *et al.* found an NSE positivity rate of 80% but did not find a variation across different organs [34].

The measurement Ki67 index by manual counting in "hot spots", has prognostic significance in GEPNET where it is used for grading in conjunction with mitotic count. In concordance with the findings of Uppin et al. [7], there was a moderate correlation between Ki67 and mitotic count using Spearman correlation analysis (r^s=0.89).

Pancreatic well differentiated nonfunctional neuroendocrine tumors in our study were larger than in previous studies [12]. A single multifocal functional pancreatic insulinoma was found, which was 1 cm in greatest dimension. Previous studies have shown most insulinomas to be smaller than 1 cm, with multifocality being seen in 10% of pancreatic NET [12].

Conclusion

Neuroendocrine neoplasms of the gastroenteropancreatic region are unique and rare tumors with malignant potential, affecting the stomach, duodenum, jejunum, ileum, rectum, appendix and pancreas, with the duodenum being the most common site. Most of the tumors are sporadic. The diagnosis by histopathology requires a high index of suspicion, especially on small biopsy as endoscopic sampling error might delay the diagnosis. Morphologic diagnosis is based on a nesting pattern and salt and pepper chromatin, with synaptophysin and chromogranin immunohistochemical staining. Clinicopathologic correlation with WHO classification and TNM staging, along with screening for lymph nodal and distant metastasis must be included for a holistic approach to the patients with gastroenteropancreatic neuroendocrine tumors.

Disclosure of conflict of interest

None.

Abbreviations

GEPNET, Gastroenteropancreatic neuroendocrine tumors; MANEC, Mixed adenoneuroendocrine carcinoma; MiNEN, Mixed neuroendocrine-non-neuroendocrine neoplasm.

Address correspondence to: Dr. Bhawana Ashok Badhe, Department of Pathology, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry, India. Tel: 7598646690; Fax: 2272068; E-mail: bhawanabdh11@gmail.com

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