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CLINICOPATHOLOGIC STUDY OF NEUROENDOCRINE TUMOURS OF GASTROINTESTINAL TRACT

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Abstract

Background: The neuroendocrine tumours (NETs)have a characteristic histologic appearance unrelated of the exact site of origin. However, the behaviour of these tumours are different in each of these sites. In this article we study the clinicopathological features of Gastrointestinal tract (GIT). These tumours were classified and graded according to WHO 2010 criteria. The immunohistochemical (IHC) features were evaluated and the grade of the tumour was correlated with Ki67. **Methods:** A total of 11 cases of diagnosed on biopsies as well as resected specimens were analysed from January 2019 to June 2023 at department of pathology, UPUMS, Saifai. It was a retrospective study included all cases of NETs of GIT with or without nodal metastasis. **Results:** Most of the tumours were well differentiated NETs (81.8% G1 and 18.2% G2). Ilium (36.3% was the most common site followed by duodenum (18.2%) and appendix (18.2%). Regional lymph node involvement was present in 18.2% of cases. On IHC synaptophysin, chromogranin-A and neuron specific enolase were positive in 100%, 81.2%% and 90.9% respectively. Ki-67/MIB-1 index was used to grade the neuroendocrine neoplasm and 81.2 % were graded as G1 NETs and 18.2 % as G2 NETs. **Conclusions:** The most common site was small intestine followed by stomach and appendix. Majority of the tumours were NET G1. On IHC SYP, CgA and NSE were positive 100%, 81.2%% and 90.9% of cases. Ki67 was helpful in grading these tumours.

Keywords: Neuroendocrine tumours (NETs); gastrointestinal tract (GIT); grade; Ki67.

INTRODUCTION

Neuroendocrine tumours (NETs) are epithelial neoplasm with predominantly neuroendocrine differentiation and originate from diffuse endocrine system located in the gastrointestinal (GI) tract and are also present in a variety of other viscera such as pancreas, lung, thyroid and adrenal gland.[1] It represents 2% of all GI tumours.[2]Endocrine cells are interspersed within the mucosa of the GIT and comprise approximately 1% of all mucosal cells.[3]NETs commonly present as polypoidal or nodular circumscribed elevations which are located within the mucosa or submucosa. The overlying mucosa can be intact or ulcerated. This is a heterogeneous group of tumours which present with variety of clinical symptoms. They can be functional or nonfunctional. According to degree of differentiation, NETs are classified as well differentiated NETs which is further divided on the basis of number of

mitosis/ki-67 index into G1 and G2, poorly differentiated neuroendocrine carcinomas (NECs) and mixed adeno neuroendocrine carcinomas.[4]

NETs show positivity for synaptophysin (SYP), chromogranin A (CgA), neuron-specific enolase (NSE), protein gene product 9.5, CD56 and leu7.[5]

Their behaviour is better in comparison to GI conventional adenocarcinomas (2). In the present study we have tried to compile the clinicopathological profile of the NETs which were diagnosed on biopsy or resection according to WHO 2010 criteria (6). We have analysed the immunohistochemical (IHC) features along with Ki67 index and also tried to correlate the grade of the tumour with Ki67 labelling index.

METHODS

All the cases of gastrointestinal neuroendocrine tumours diagnosed at Department of Pathology, Uttar Pradesh university of Medical Sciences, Saifai, Etawah from January 2019 to June 2023 were analysed. The demographic data and clinical details were retrieved from the medical records. The haematoxylin and eosin (H & E) stained sections were reviewed and histomorphological features including the cellular arrangement and cell morphology pertaining to the various sites were analysed in all the cases. The diagnosis of neuroendocrine tumour was made on both biopsies as well as resected specimens. The classification and grading of these tumours were done according to WHO 2010 classification [6]. IHC was done with chromogranin, synaptophysin and Neuron specific enolase respectively. Ki67 was done in all cases. All the primary antibodies (chromogranin, synaptophysin, pan cytokeratin and Ki67) were ready to use, mouse monoclonal antibodies supplied by Bio Genex, CA. IHC were performed on fully automated immunostainer (i6000; Bio Genex) by using poly horse radish peroxide (HRP) technique.

RESULTS

There were 11 cases of NET diagnosed in the study period which included 6 male and 5 female patients in the age range of 34 to 72 years (mean: 54.5 years) Majority of them (8 cases, 72,2%) were >45 years of age. Biopsy diagnosis was mostly made in NETs of GI tract.

Clinical features

All the cases were non-functional and most common presentation was abdominal pain, loss of weight and loss of appetite. None of the cases presented with carcinoid syndrome or symptoms related to hormonal secretion. All were sporadic cases of NET and syndromic association with MEN was not identified. The clinical features are summarized in Table 1.

Table 1: Clinical features of neuroendocrine tumours (NET)

Symptoms	No of cases	percentage
Pain abdomen	6	54.5%
GI Bleed	1	9.1%
Vomiting	3	27.3%
Loss of weight	6	54.5%
Loss of appetite	5	45.5%

Location

GI NETs were identified in 11 patients. Ilium (36.3% was the most common site followed by duodenum (18.2%) and appendix (18.2%) [table 2]. Regional lymph node involvement was present in 2 cases (18.2%).

Table 2: Distribution according to the site

Site	No of Cases	Percentage
Ilium	4	36.3%
Duodenum	2	18.2%
Appendix	2	18.2%
Rectum	1	9.1%
Stomach	1	9.1%
Colon	1	9.1%

Size of the tumour ranges from 2cm to 8 cm with most tumours in the range of 3-4 cm (54.5%). Most of the tumours were polypoidal lesions 7 cases (63.6%)

Most of the tumours were well differentiated NETs (81.8% G1 and 18.2% G2). The most frequent pattern of cellular arrangement was that of islands and lobules of tumour cells[fig1a]. The cells showed characteristic monomorphic nuclei with stippled chromatin and granular eosinophilic cytoplasm[fig1b]

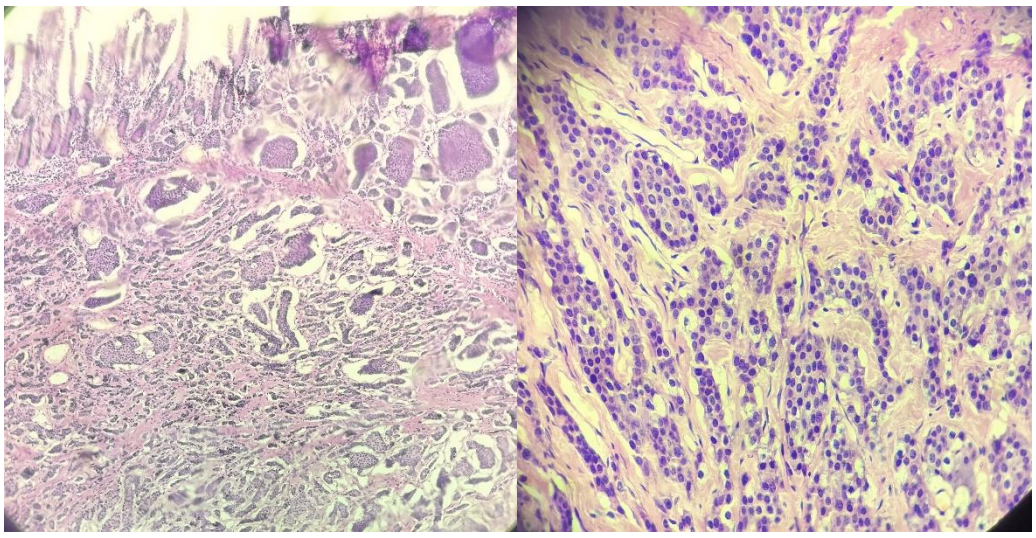

Fig 1a: Section from ilium shows islands and tubules of tumour cells.

Fig 1b: The cells show monomorphic nuclei and granular eosinophilic cytoplasm.

On IHC synaptophysin, chromogranin-A and neuron specific enolase were positive in 100%, 81.2%% and 90.9% respectively [Fig 2a, 2b and 2c].

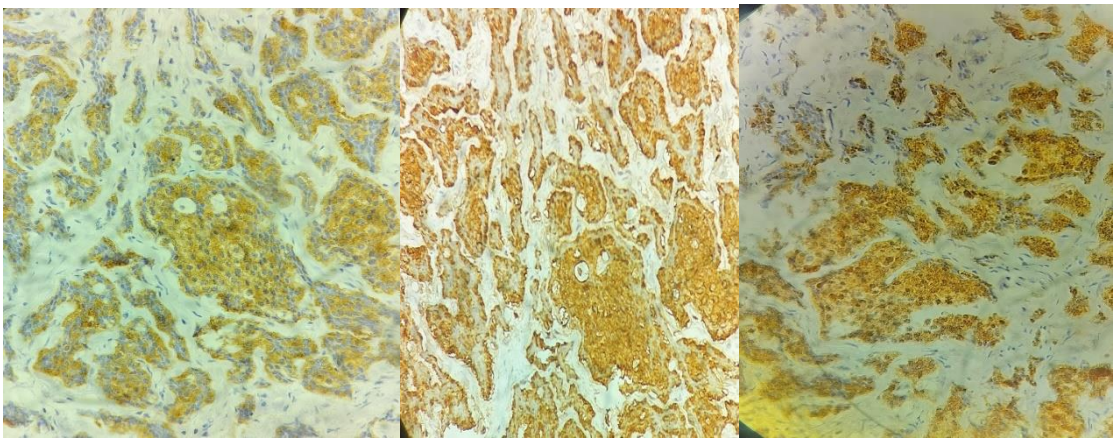

Fig 2a, 2b and 2: Cytoplasmic positivity for synaptophysin, chromogranin and neuron specific enolase

Ki-67/MIB-1 index was used to grade the neuroendocrine neoplasm and 81.2 % were graded as G1 NETs [Fig 3] and 18.2 % as G2 NETs

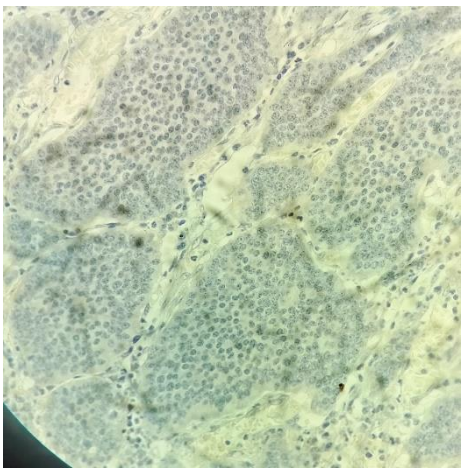

Fig 3: Ki67 less than 10%

DISCUSSION

According to Sippel et al.,[7] the estimated prevalence of NETs is 1–2 cases per 100,000 people, of which GI tract is the most common site.[8] The NETs of GIT are rare neoplasms, but their incidence has been increasing probably because of advancement in various diagnostic modalities. The main aim of the study was focused on these rare tumours. The most common age group in our study was 51–60 years and comprised 5 cases (45.5%), followed by 41–50 years 3 cases (27.3%%) , with a mean age of 54.5 years and an age range of 34-72 years. This is comparable to a study done by Amarapurkar et al. [2] who reported the mean age as 53.01 years (range 16–82 years) and majority of the patients were between 41 and 60 years. Similar results were reported by Zeng et al. [8] who conducted a study comprising 122 patients in Japan between 2000 and 2011, reported the mean age as 49.13 ± 16.21 years.

Out of the total of 11 cases of NENs, 6 were from males (54.5%) and 5 were from females (45.5%) Zeng et al. [8] reported a slight female predominance but in our study slight male predominance may be due to small sample size. Pain abdomen was the main symptom in our study and was present in 54.5% (6/11 patients) followed by loss

of weight and loss of appetite. In a study by Zeng et al.,[8] abdominal pain was the most common symptom which was present in 99 patients out of a total of 122 patients (77.9%). In a study by Niederle et al.,[9] the most common presenting symptom was abdominal pain (29.5%). In the present study, the most common site was ilium, comprising 4 cases out of a total of 11 cases (27.5%), followed by duodenum (18.2%) and appendix. Estrozi et al. [10] who also found stomach as the most involved site (24.5% or 190/773 cases) followed by small intestine (161 cases or 20.8%). In a study by Niederle et al.,[9] the most common site of the primary was stomach 22.8% (65/277) followed by appendix 20.7% and small intestine (15.4%). NETs in the present study were analysed immunohistochemically for expression of CgA, SYP, NSE, and Ki-67/MIB-1. All 11 cases (100%) showed positivity for SYP, 10 cases (90.9%) showed positivity for NSE, and 9 cases (81.2%) cases showed positivity for CgA. These three markers showed cytoplasmic positivity (fig 2a, 2b and 2c).

Zeng et al. [8] in their study, 81.1% of cases were positive for CgA, 87.7% for SYP, and 57.4% for NSE. In a study by Lee et al.,[11] 96% of the tumours showed positive reaction for SYP and 44% of the tumours showed positive reaction for CgA. Yucel et al. [12] conducted a study comprising 52 patients and found that the most frequently used IHC stains were CgA, SYP, and NSE stains. Thirty-six (92%) patients were positively stained with CgA, 38 (95%) patients were positively stained with SYP, and 21 (71%) patients were positively stained with NSE. According to a few other studies conducted by Shayanfar and Shahzadi[13] and Korse et al.,[14] they reported that there was a correlation between the staining characteristics of the tumour and the grade of the tumour and CgA positive staining was seen mostly in well-differentiated NETs whereas NSE-positive staining was seen in poorly differentiated NETs. However, in our study, we did not find any significant association between the grade of the NENs and the IHC staining pattern of these markers. In our study, we had 9 cases (81.2%) of well-differentiated NETs G1 followed by 2 cases (18.2%) of well-differentiated NETs G2 [Figures 7-9]. No case of neuroendocrine carcinoma was reported in our study.The tumours were graded according to the WHO 2010 guidelines which are based on the number of mitotic figures and/or the Ki-67/MIB-1 index. Zeng et al.,[8] they found that G1 tumours comprised 55.7% of cases (68/122), G2 comprised 26.2% of cases (32/122), and 18.1% of cases (22/122) were G3 tumours. In a study conducted by Lim et al.,[15] the most common histological grade was G1 (74.5%) followed by G2 (13.7%) and G3 (11.8%). In our study, 2 cases (18.2%%) showed evidence of regional nodal metastasis. This is comparable to a study conducted by Amarapurkar et al. [2] in which the regional spread was seen in 14/74 cases (18.9%). There are few limitations in our study most prominently is limited size of patient population.

CONCLUSION

The most common site was small intestine followed by stomach and appendix. Majority of the tumours were NET G1. On IHC SYP, CgA and NSE were positive 100%, 81.2%% and 90.9% of cases. Ki67 was helpful in grading these tumours and elucidation of these features will facilitate early diagnosis and improve the accuracy of grading of tumours to predict the therapy and outcome of the disease.

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