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HISTOPATHOLOGICAL PROFILE OF GASTROINTESTINAL NEUROENDOCRINE TUMORS IN A TERTIARY CARE HOSPITAL

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Background. *Recently there has been a lot of discussion about the terminology and classification of neuroendocrine tumours of the gastrointestinal tract. The WHO has recommended a change of terminology and classification of these tumours. In 2019 a significant update was done in the WHO classification of neuroendocrine tumours of GIT in which neuroendocrine carcinomas (NECs) are all considered high-grade tumours. Previously, grade 1 and 2 tumours were regarded as neuroendocrine tumours (NETs) and grade 3 neoplasms as NECs. The new classification avoids confusion between these two clinically and molecularly distinct notions.*

Objective. *The aim of the research was to study GI neuroendocrine neoplasms and classify them as per location and Histopathological classification of GI neuroendocrine neoplasms according to the recent WHO classification. To use IHC whenever and wherever required for categorization of GI NET's.*

Methods. *Over a period of 15 years, a total of 85 cases of neuroendocrine neoplasms of GIT were studied. The histopathological material of patients was reviewed and histopathological diagnosis confirmed. Paraffin embedded tissue blocks were used to study and review the material. Sections from tissue blocks were stained. Five-micron sections were cut and stained. The sections were stained using DAKO LSAB-2® system HRP glass slides coated with 0.5% poly-lysine.*

Results. *Out of 85 cases 40 involved male and 45 female patients. The mean age was 46.4 years; age range 9-85 years. In our study, appendix 24 (28.23%) and stomach 11 (12.95%) were the commonest sites of primary involvement followed by colon (10), ileum (10), duodenum (5), GE junction (5), jejunum (3), oesophagus (2), rectum (2) and gall bladder (1). Metastasis to the liver were observed in 12 patients with known and unknown primary diagnosis. Based on the latest WHO classification 5 patients were classified under NECs and the rest under NETs.*

Conclusions. *Neuroendocrine tumours (NETs) are uncommon malignancies of GIT. Appendix followed by stomach was the most common anatomical site. NET Grade 1 was the most common histological type. IHC markers NSE, Synaptophysin and Chromogranin can be used in diagnosis of NETs.*

KEYWORDS: carcinoid; neuroendocrine tumours; neuroendocrine carcinoma; IHC; histopathology.

Introduction

Gastrointestinal endocrine tumours currently referred to as gastrointestinal neuroendocrine tumours (GI-NETs), were known as carcinoids previously [1-4]. Accumulation of evidence has given way for newer and updated classification [4-6]. NENs account for about 0.5% of newly diagnosed neoplasms [7]. An increase in frequency of carcinoids is being noticed possibly as a result of increased ascertainment of cases from the ever-increasing use of diagnostic techniques [8]. The majority are well-differentiated neoplasms that can be diagnosed easily by traditional light microscopy and routine immunohistochemistry, but a small proportion can cause diagnostic difficulty. Gastrointestinal neuroendocrine tumours (GI-NETs) are currently sub-classified on morphologic grounds into Well differentiated NETs (WD-NETs) that have an indolent clinical course and the poorly differentiated ones that, on account of their outspoken malignant characteristics and aggressive clinical behaviour, are designated as poorly differentiated neuroendocrine carcinomas (PD-NECAs). In this classification, tumours that were referred to as carcinoids would correspond to the WD-NETs. In routinely processed tissue sections, these neuroendocrine cells can be conveniently identified histochemically by their argentaffin or argyrophil properties or immunohistochemically by staining for such generic neuroendocrine markers as chromogranins, synaptophysin,

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neuron-specific enolase (NSE) and PGP9.5 etc. that relate to their neurosecretory granules, cytosol, or vesicles. Specific cell types such as serotonin-producing EC cells, histamine-producing ECL cells, gastrin-producing G cells, or Somatostatin producing D cells, etc. are similarly best identified by the immunohistochemical localization of their secretory products in their cytoplasm. Previously neuroendocrine tumours were classified on the basis of site which led to divergence in terminologies and criteria. So, in 2010 a new WHO classification was published for neuroendocrine neoplasms. The main feature of this new classification system is the distinction between well-differentiated NETs and poorly differentiated NECs. Although NETs and NECs are not closely related neoplasms, they share the expression of neuroendocrine markers [1-3]. In this classification NETs are graded into G1, G2, and G3 based on mitotic rate and/or Ki-67 proliferation index. The mitotic rates used for grading NETs are expressed as the number of mitoses/mm^2, which is assessed by counting in 50 fields of 0.2 mm^2. Although the mitotic rate yields an accurate assessment, it may be unreliable for small samples. To determine the Ki-67 proliferation index, at least 500 cells in the regions of highest labelling, known as "hotspots", are counted. These areas are identified via scanning magnification. When areas with two varying proliferation indices are present in a particular sample, the area with higher proliferation index is selected for grading purposes [3, 9-13]. NECs are subtyped into small-cell NEC (SCNEC) and large-cell NEC (LCNEC). By definition, NECs are always high-grade neoplasms. Hence, as per the new WHO classification, NECs are not assigned any grade to avoid any confusion with neuroendocrine tumours in the G3 category (Table 1). In this single centre study, our objective was to study GI neuroendocrine neoplasms and classify them as per location. The tumours according to the recent WHO classification were further classified. We used IHC whenever and wherever required for categorisation of GI NET's.

Methods

The study period was 15 years. The histopathological material of patients was reviewed and histopathological diagnosis was confirmed.

Table 1. The 2019 World Health Organization (WHO) classification for neuroendocrine neoplasms (NEN) of the digestive tract

Well-Differentiated NEN	Ki–67 Index (%)	Mitotic Index (HPF)
NET G-1 (low-grade)	<3	<2/10
NET G-2 (intermediate-grade)	3–20	2–20/10
NET G-3 (high-grade)	>20	>20/10
Poorly differentiated NEN		
NEC G-3 Small-cell type, Large-cell type	>20	>20/10
Mixed Neuroendocrine–nonneuroendocrine neoplasm (MiNEN)		

Notes: NEN – neuroendocrine neoplasms, HPF – high-power fields, NET – neuroendocrine tumours, NEC – neuroendocrine carcinomas.

Table 2. Distribution of cases as per location

Site	Number
Appendix	24
Stomach	11
Colon	10
Ileum	10
Duodenum	5
GE Junction	5
Jejunum	3
Oesophagus	2
Rectum	2
Gall bladder	1
Secondaries to liver	12
Total	85

The medical records of patients were reviewed and primary site of involvement of GI tract was confirmed. The specimens preserved in the Department of Pathology were used to study the gross appearance of the tumours and further material obtained from specimens and processed as and when needed. Paraffin embedded tissue blocks were used to study and review the material. Sections from tissue blocks were stained for immunostains and hematoxylin and eosin (H&E). The corresponding slides for the respective cases were used to study and classify the cases based on morphology. For the prospective material the specimens received fresh were fixed in 10% formalin. After adequate fixation representative bits were given. The tissue bits were processed and embedded in paraffin for pathological examination. Five-micron sections were cut and stained. Immunohistochemical studies were carried out using 5-micron paraffin sections. The sections were stained using DAKO LSAB-2® system HRP glass slides coated with 0.5% poly-lysine.

Results

A total of 85 cases were found, out of which 40 were males and 45 were females. Mean age was 46.4 years with age ranging 9-85 years old. Table 2 gives the details of tumours origin.

Gastric neuroendocrine tumours were further classified into type 1, 2 and 3 on the basis of endoscopic and histology findings. Among 11 cases, 8 were type 1, 2 were type 2 and 1 case was type 3 (Fig. 1 and 2). Fig. 3-5 show histopathology and immunohistochemical details using different stains employed in our study.

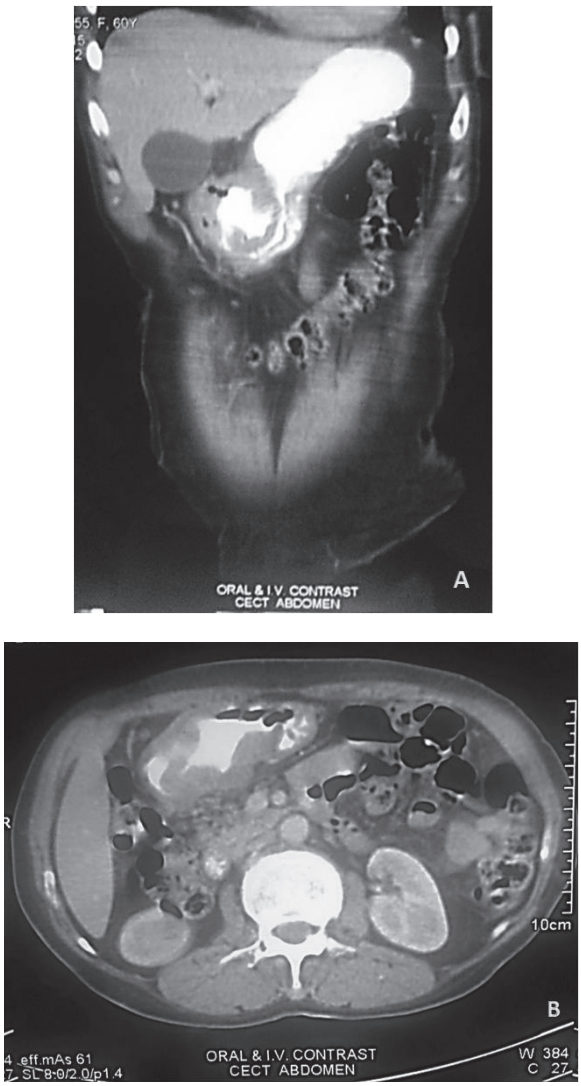

Fig. 1. *Distended stomach showing circumferential thickening and mass within gastric wall with peri-gastric fat infiltration and lymphadenopathy on CECT.*

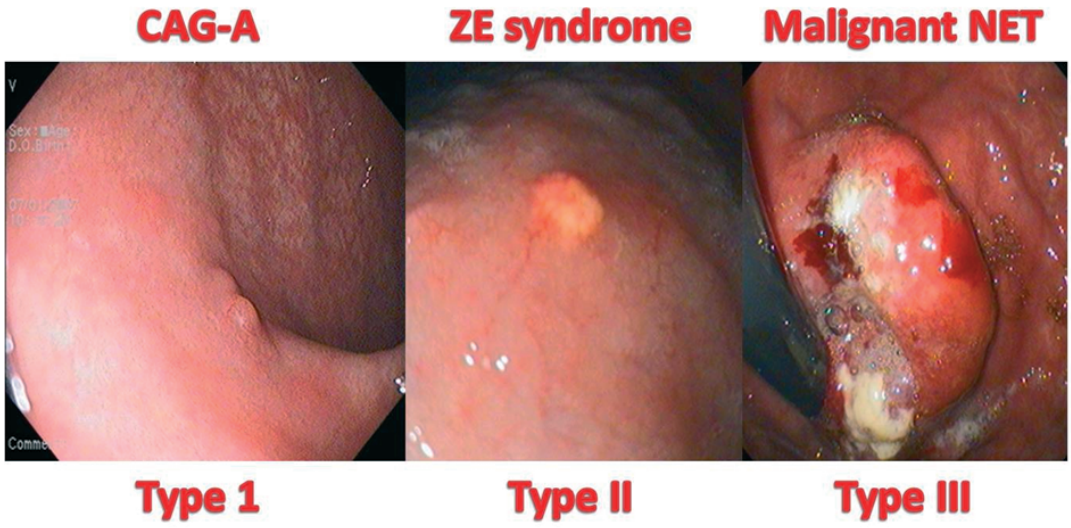

Fig. 2. *Showing endoscopic picture of gastric neuroendocrine tumours*

Table 3. Distribution of cases as per grading

Grade	NO. OF CASES
Well-Differentiated NEN	
NET G-1 (low-grade)	38
NET G-2 (intermediate-grade)	32
NET G-3 (high-grade)	10
Poorly differentiated NEN	
NECG-3 Small-cell type, Large-cell type	5
Mixed Neuroendocrine-nonneuroendocrine neoplasm (MiNEN)	

Notes: NEN – neuroendocrine neoplasms, HPF – high-power fields, NET – neuroendocrine tumors, NEC – neuroendocrine carcinomas.

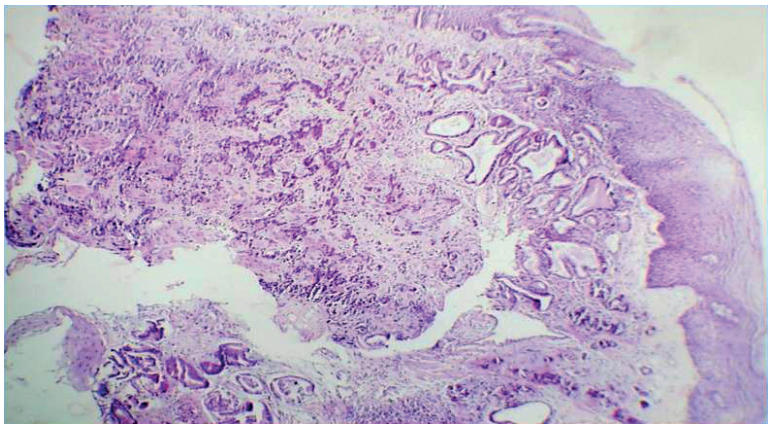

Fig. 3. *Low power view of a neuroendocrine tumour in esophagus.*

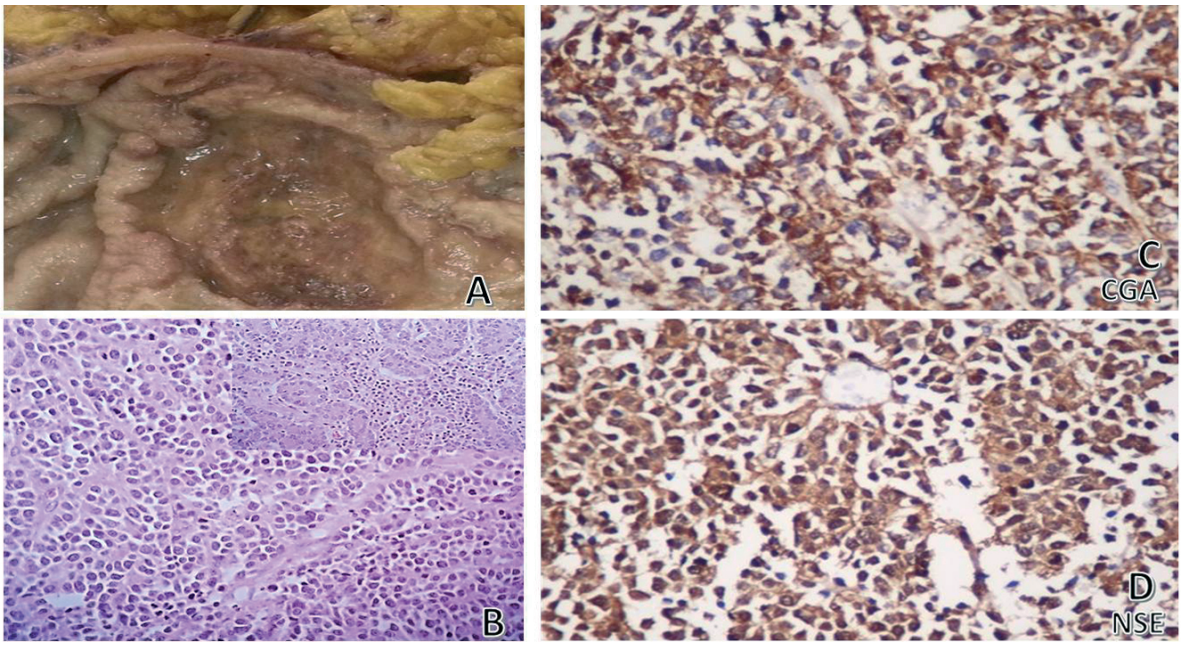

Fig. 4. A. *Gross photomicrograph of gastrectomy specimen showing a large ulcerated growth infiltrating into serosa.*
B. *(H&E 400X): Small to medium sized tumour cells with scant to moderate cytoplasm, salt and pepper chromatin with tumour cells arranged in sheets trabeculae and rosettes (inset).*
C. *(Chromogranin A; CGA): Tumour cells stained strongly positive for chromogranin A.*
D. *(neuron specific enolase; NSE): Tumour cells stained strongly positive for NSE.*

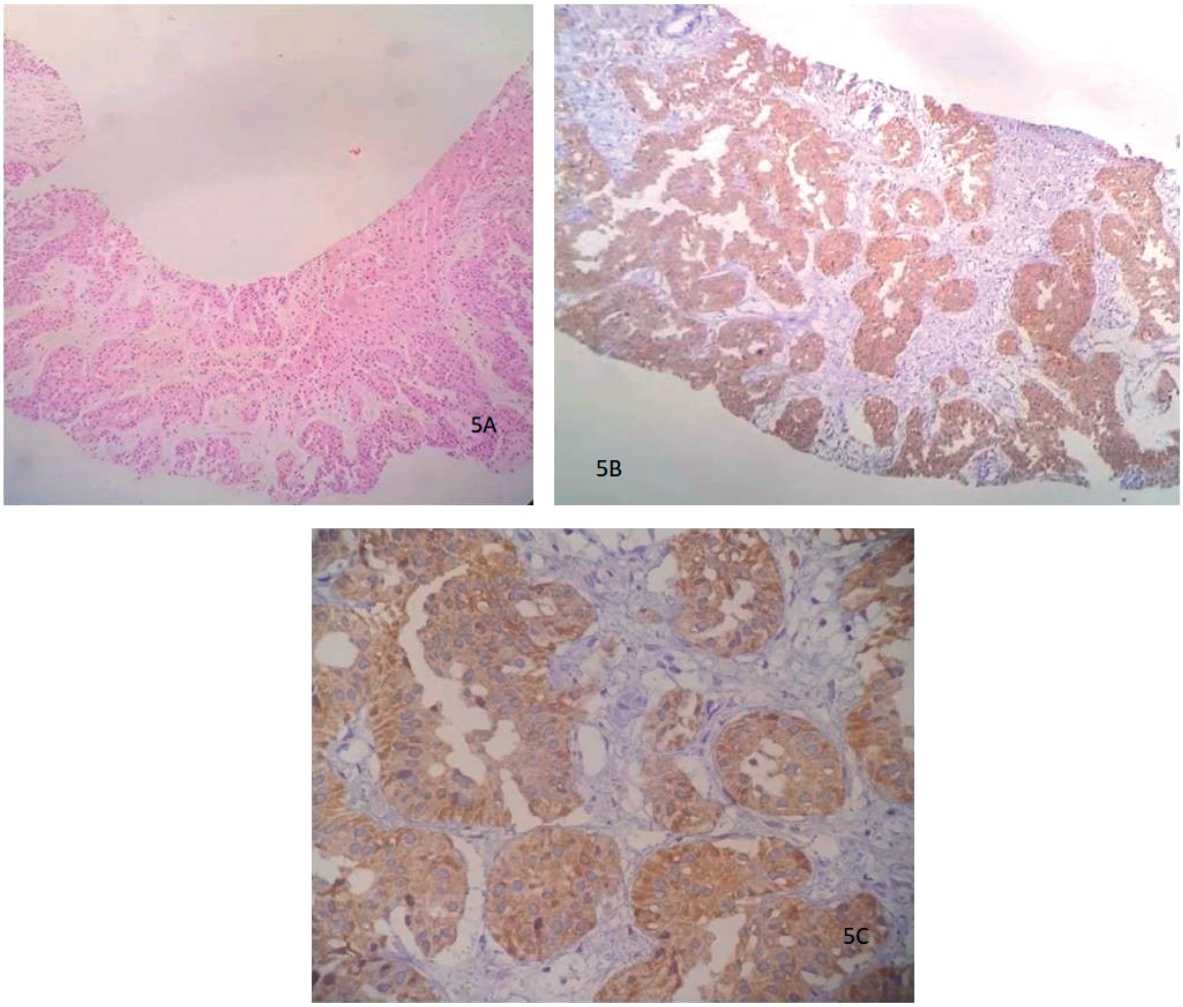

Fig. 5. A. *(H&E): Shows deposits of a tumour in liver with cells arranged in acinar and nesting pattern.*
B. *(neuron specific enolase NSE): Tumour cells show positivity for synaptophysin.*
C. *(synaptophysin): Tumour cells show positive staining for synaptophysin.*

Discussion

Neuroendocrine tumours of the gut have been also called as carcinoids ever since Oberndorfor coined this term to designate tumours that resembled carcinomas but behaved as if they were benign. Using 'carcinoid' as a collective term has certain limitations that this term does not differentiate benign from malignant tumours, morphologically identical tumours at different sites can show divergent prognosis and the cell of origin can be different in all tumours. The tumours arising from these cells differ in their respective locations, etiological factors, pathogenesis and also prognosis. The mean age at diagnosis of NET of GIT in the present study was 46.4 years. Similar results were observed in studies by Rothenstein J et al [14] Bruna Estrozi et al [15] and Amarapurkar DN et al [16] where the mean age at diagnosis was 56, 52.8 and 53 respectively. The studies by Rothenstein J et al and Amarapurkar DN et al showed that males were more commonly involved with neuroendocrine tumours of GIT as in our study [14,16]. Most of the patients presented with nonspecific symptoms of abdominal pain and vomiting. Similar findings have been noted by Amarapurkar et al, who reported 74 cases of NETs of GIT-pancreas [16]. It was found out that the appendix was the most common site of primary NENs followed by the stomach, however in the study by Klimstra et al the ileum and appendix have been reported as the most common sites for NET [17]. Maggard et al found the small intestine to be the most common site accounting for 44.7% [18]. Amarapurkar et al found that the stomach (30.2%) was the most common site followed by the pancreas (23.3%) [16]. In our study NET G1 was the most common histologic type followed by NET G2 and neuroendocrine carcinomas

respectively that correlated with the literature where Rothenstein J et al and Amarapurkar et al also found NET G1 as the most common tumour [14,16]. Similarly, according to Matsui K et al [19] and Okita NT et al [20], neuroendocrine carcinoma is a rare tumour with highly malignant biological behaviour exhibiting aggressive growth that leads to vascular invasion, distant metastasis and poor prognosis [19,20]. Our results were similar to the study by Amarapurkar et al in which Metastasis was seen in 18.9% of cases and Yamaguchi et al. who reported metastatic deposits in 7 out of the 45 cases (15.5%) [16,21]. Immunohistochemical studies were used to confirm the diagnosis of neuroendocrine tumours. Our study also showed that NSE and synaptophysin were expressed by most of the tumours compare to chromogranin. Anna Fen-Yau Li et al also found that NSE and synaptophysin were useful markers in confirming Neuroendocrine tumours. [22].

Conclusions

Neuroendocrine tumours (NETs) are uncommon malignancies of GIT. The appendix followed by the stomach was the most common anatomical site. NET Grade 1 was the most common histological type. IHC markers NSE, synaptophysin and chromogranin can be used in diagnosis of NETs.

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Conflict of interests

Authors declare no conflict of interest.

Authors contributions

Dr. Farhat Abbas and Dr. Mehnaaz Sultan Khuroo – conceptualization, methodology, formal analysis, writing – original draft, writing – reviewing and editing; *Dr. Ambreen Beigh and Dr. Summyia Farooq* – data curation, writing – reviewing and editing; *Dr. Naira Sultan Khuroo and Dr. Shagoofa Tazeen* – investigation, formal analysis.

ГІСТОПАТОЛОГІЧНИЙ ПРОФІЛЬ НЕЙРОЕНДОКРИННИХ ПУХЛИН ШЛУНКОВО-КИШКОВОГО ТРАКТУ В МЕДИЧНИХ ЗАКЛАДАХ ТРЕТИННОГО РІВНЯ

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Вступ. *Останнім часом ведеться багато дискусій щодо термінології та класифікації нейроендокринних пухлин шлунково-кишкового тракту. ВООЗ рекомендувала змінити термінологію та класифікацію цих пухлин. У 2019 році було внесено значне оновлення в класифікацію ВООЗ нейроендокринних пухлин шлунково-кишкового тракту, в якій усі нейроендокринні карциноми (NEC) вважаються новоутвореннями високого ступеня тяжкості. Раніше пухлини 1 і 2 ступеня вважалися нейроендокринними пухлинами (NET), а новоутворення 3 ступеня – NEC. Нова класифікація дозволяє уникнути плутанини між цими двома патологіями різними на клінічному та молекулярному рівнях.*

Мета. *Вивчити нейроендокринні новоутворення шлунково-кишкового тракту та класифікувати їх за локалізацією та гістопатологічною класифікацією нейроендокринних новоутворень шлунково-кишкового тракту за останньою класифікацією ВООЗ. Для категоризації нейроендокринних новоутворень шлунково-кишкового тракту використовували імуногістохімічний метод.*

Методи. *Протягом 15 років досліджено 85 випадків нейроендокринних новоутворень ШКТ. Вивчався гістопатологічний матеріал пацієнтів та підтверджувався гістопатологічний діагноз. Для вивчення та перегляду матеріалу використовувалися тканинні блоки просочені парафіном. Зрізи товщиною 5 мікронів фарбували на предметному склі покритому 0,5% полілізином за допомогою системи HRP DAKO LSAB-2®.*

Результати. *З 85 випадків 40 були чоловіками та 45 жінками. Середній вік становив 46,4 року; віковий діапазон 9-85 років. У нашому дослідженні апендикс 24 (28,23%) і шлунок 11 (12,95%) були найчастішими місцями первинного ураження, за ними слідували товста кишка (10), клубова кишка (10), дванадцятипала кишка (5), гастроезофагальне з'єднання (5), тонка кишка (3), стравохід (2), пряму кишку*

(2) і жовчний міхур (1). У 12 пацієнтів з відомим і невідомим первинним діагнозом спостерігалися метастази в печінку. На основі останньої класифікації ВООЗ 5 пацієнтів були віднесені до NEC, а решта – до NET.

Висновки. *Нейроендокринні пухлини (NET) є рідкісними злоякісними новоутвореннями шлунково-кишкового тракту. Апендикс і шлунок уражалися найчастіше. NET 1 ступеня були найпоширенішим гістологічним типом. Імуногістохімічні маркери NSE, Synaptophysin і Chromogranin можуть бути використані в діагностиці NET.*

КЛЮЧОВІ СЛОВА: карциноїд; нейроендокринні пухлини; нейроендокринна карцинома; імуногістохімічний метод; гістопатологія.

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