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AUDIT ARTICLE

Gastroenteropancreatic neuroendocrine tumours: Clinicopathological evaluation at Shifa International Hospital, Islamabad

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Abstract

Objective: Clinicopathological features of gastroenteropancreatic neuroendocrine tumours (GEP-NETs) have rarely been studied in Pakistani population. We investigated clinical characteristics of these tumours according to updated World Health Organization (WHO) 2010 classification.

Methods: The data of Shifa International Hospital, Islamabad was retrospectively analysed for pathologically confirmed GEP-NETs from January 2013 to March 2018.

Results: One hundred and eighteen patients (mean age, 52.2± 16.4 years; Of these 65(55.1%) were males. Majority, 98(83.1%) of the patients were symptomatic including 6(5.1%) with functional tumours. Pancreas was the most frequent primary site noted in 33(28%) patients. The most common histologic type was well differentiated neuroendocrine tumour (WDNET) in 96(81.4%) patients followed by neuroendocrine carcinoma (NEC) in 11(16.1%) patients. Almost half the cases or 54(45.8%) of WDNET were grade 1, 32 (27.1%) were grade 2, and 10 (8.5%) were grade 3. Distant metastasis at the time of diagnosis was found in 18(15.3%) cases with 14,(77.7%) in liver as the most common metastatic site. Synaptophysin positivity was seen in 60 (96.8%) cases of grade 1, 32(27.2%) of grade 2 WDNET, 8(100%) cases of grade 3 WDNET and 12(92.3%) of NEC and chromogranin was positive in 49(94.2%) of grade 1 and grade 2 WDNET, 5 (83.3%) cases of grade 3 WDNET and 5 (45.4%) cases of NEC.

Conclusion: GEP-NETs showed a wide clinicopathological spectrum. Pancreas is the most common site of involvement by the GEP-NET, however, grade 3 WDNET had a predilection for colon. Small cell carcinoma was commonly observed in the oesophagus.

Keywords: Gastroenteropancreatic neuroendocrine tumour, well differentiated neuroendocrine tumor, neuroendocrine carcinoma. (JPMA 71: 492; 2021) **DOI: https://doi.org/10.47391/JPMA.835**

Introduction

Gastroenteropancreatic neuroendocrine tumours (GEP-NETs) are rare neoplasms that arise from neuroendocrine cells scattered diffusely in gastrointestinal tract as well as endocrine cells embedded in pancreas.[1] These tumours are characterized by a varied and wide spectrum of clinical behaviour, encompassing a well differentiated, indolent tumour to highly malignant, rapidly metastasizing poorly differentiated malignancy.[2]

The clinical presentation of patients with GEP-NETs is dependent on functional status of the tumour. The non-functioning tumours are more common and their symptoms surface due to local mass effect or distant metastasis, which includes abdominal pain, intra-abdominal mass, weight loss, jaundice etc. Patients with functioning tumours are mostly seen in pancreas where symptoms become apparent by release of specific hormones by the tumour.[3]

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The nomenclature of neuroendocrine tumours (NET) is generally based on the organ in focus. However, a uniform classification has matured for NET of gastroenteropancreatic region by World Health Organization (WHO)[4] According to WHO, GEP-NETs are generally categorized into two broad groups:

1. Well differentiated neuroendocrine tumour (WDNET) demonstrates a characteristic architecture on histology that includes trabeculae, nests, glandular formation, gyriform, pseudorosettes and solid etc. Historically they were referred to as carcinoid tumours, but due to their apparent confusion with clinically functional tumours, this name is now not in use anymore.[5]

2. Neuroendocrine carcinoma (NEC), which includes large cell neuroendocrine carcinoma (LCNEC) and small cell neuroendocrine carcinoma (SCNEC) show undifferentiated or high grade histology on light microscopy and a poor clinical course.[6]

The 2010 WHO grading scheme of GEP-NET was solely based on proliferative index (mitotic count and/or Ki-67 index), thus dividing NET into three grades. Grade I (<2% Ki-67 index) and grade 2 (3% to 20% Ki67 index) were consistent with WDNET, while all grade 3 NET (>20% Ki67

index) irrespective of histological architecture were incorporated into NEC.[7] A recent modification in the said classification has incorporated tumour architecture along with mitotic rate for grading of these tumours. This modification has followed various studies, which reported high grade NET with raised mitotic index (>20%Ki-67 index) but architectural differentiation favouring NET. These tumours are reported to behave better in terms of survival when compared with NEC but have a more dismal prognosis than grade 2 WDNET. Thus grade 3 NET are now divided into 2: WDNET grade 3 (characteristic architectural features and a Ki-67 index more than 20%) and NEC (undifferentiated pattern with a Ki-67 index more than 20%).[2,8]

Although they are rare tumours but their prevalence has increased substantially over past three decades, possibly due to increased awareness and advanced diagnostic modalities. The age-adjusted incidence of GEP-NETs has increased 3.65-fold in the USA and 3.8- to 4.8-fold in the UK.[9] In Pakistan, data regarding incidence of neuroendocrine tumours is not readily available. In 2016, the Aga Khan University Hospital reported neuroendocrine differentiation in 2.5% of the total GI malignancies while annual cancer registry of SKMCH showed this figure to be 5.2%.[10,11]

Increased research regarding neuroendocrine tumours has led to improved and newer treatment strategies and constant update on histopathological diagnosis. Since recent modification in WHO 2010 classification fewer studies have reported its application. The objective of this retrospective study was to share our analysis of GEP-NETs at Shifa International Hospital, Pakistan according to new WHO classification.[4]

Materials and Methods

The data of Shifa International Hospital, Islamabad was retrospectively analysed for GEP-NETs after approval from Institutional review board and ethics committee of Shifa International Hospital, from January 2013 to March 2018. All patients diagnosed with WDNET, NEC, SCNEC, LCNEC from gastrointestinal tract and functional and non-functional endocrine tumours of pancreas were included. Epithelial tumours and metastatic NET to gastroenteropancreatic region were excluded.

The clinicopathological characteristics of patients noted from their medical records included: age, gender, and primary location of tumour, functional status of tumour, histological type and grade of tumour, distant metastasis and immunohistochemical status. The histological type and tumour grade were assigned according to the new WHO 2010 classification and Union for International Cancer Control (UICC)[11] of American Joint Committee on Cancer. According to this classification, a WDNET showing a characteristic histological features were assigned three grades as follows: grade 1 with a mitotic count of <2 per 10 high power fields (HPF) and/or a Ki-67 index <2%; grade 2, with a mitotic count of 2 to 20 per 10 HPF and/or a Ki-67 index of 3 to 20%; and grade 3, with a mitotic count of >20 per 10 HPF and/or a Ki-67 index >20%. Tumours that were high grade, showing an undifferentiated pattern, with a mitotic account of more >20 per 10 HPF and/or a Ki-67 index >20%, and showed positivity for neuroendocrine markers were diagnosed as NEC. High grade tumours with a small cell size showing hyperchromatic, indistinct nucleoli and nuclear moulding were diagnosed as SCNEC. The mixed adenoneuroendocrine carcinomas (MANEC) consisted of both components of adenocarcinoma and neuroendocrine tumour, and each comprising of more than 30 percent of the tumour population.

Results

Analysis of our data from January 2013 to March 2018 revealed 118 GEP-NETs. Fifteen patients diagnosed with metastatic neuroendocrine tumour on liver biopsies were excluded from the study since their primary site biopsies could not be retrieved. The mean age of patients at the time of diagnosis was 52.2 ±16.4 years (age range: 8-78 years) with a slight predominance of males (n= 65, 55.1% versus females n= 53, 44.9%) and a male to female ratio of 1.2:1. The maximum patients, 32(27.1%) were in 6th decade of life followed by 7th decade (n=26, 22%) and 5th decade (n= 22, 18.6%). Only 20(16.9%) patients had an incidental NET, while 98 (83.1%) symptomatic patients had different abdominal complaints in the form of pain, mass lesion or obstructive jaundice. Functional tumour was identified in 6(5.1%) patients encompassing 4 insulinomas and 2 gastrinomas. Pancreas,33(28%)patients, was the most frequent primary site noted followed by stomach in17 (14.4%) (Table 1). Also pancreas and colonic tumours were more common in males while duodenal tumours in 10(71%) patients were commonly seen in females. Duodenal tumours were encountered mostly in the 6th decade, while tumours in appendix were diagnosed in a younger age group (20-40 years).

The most common histologic type was WDNET in 96 (81.4%) cases, followed by NEC in 19(16.1%) cases that included Neuroendocrine carcinoma not otherwise specified (NEC-NOS) in 11 (57.8%), SCNEC in 7 (36.8%), 1(5.2%) case of LCNEC (Table 2) and 3 cases (2.5%) were MANEC.

Almost half, 54 (45.8%) cases of WDNET were grade 1, 32 (27.1%) cases were grade 2, and 10 (8.5%) cases were grade 3.

Table-1: Primary site of neuroendocrine tumours.

Tumor site	n (%)
Anal canal	1 (0.8)
Appendix	11 (9.3)
Caecum	5 (4.2)
Colon	5 (4.2)
Duodenum	14 (11.9)
Oesophagus	7 (5.9)
Ileocaecal junction	2 (1.7)
Ileum	5 (4.2)
Jejunum	3 (2.5)
Pancreas	33 (28.0)
Periampullary region	8 (6.8)
Rectum	7 (5.9)
Stomach	17 (14.4)

Table-2: Histological type and grade according to 2010 WHO classification.

Histological type & grade	n (%)
Well differentiated neuroendocrine tumour	96 (81.4)
Grade I	54 (45.8)
Grade II	32 (27.1)
Grade III	10 (8.5)
Neuroendocrine carcinoma	19 (16.1)
NEC- Unclassified	11 (57.8)
Small cell carcinoma	7 (36.8)
Large cell carcinoma	1 (5.2)
Mixed adenoneuroendocrine	3 (2.5)

Low grade WDNET (grade 1 & 2) were frequently localized in pancreas (n= 26), stomach (n=12) and rectum (n= 6) while majority of the grade 3 WDNET had their primaries in colon (n= 4). NEC were more common in pancreas (n= 5) and stomach (n= 3) while SCNEC were more common in oesophagus, 5 patients. Distant metastasis at the time of diagnosis was encountered in 18(15.3%) patients which included 13.6% of grade 1 & 2, 20% of grade 3 and 21% of NEC. The most common site of metastasis was liver in 14(77.7%) patients, while 4 cases had abdominal wall and lung metastasis. Pancreas was the most frequent primary site of the tumour that showed distant metastasis, seen in 12(66.6%) cases. Only 6 (5.0%) patients displayed synchronous tumours that included 4 adenocarcinomas of stomach and 2 hepatocellular carcinoma.

Synaptophysin and chromogranin were the most commonly applied immunohistochemical markers for confirmation of neuroendocrine differentiation. Out of 67 cases, in which both of these markers were applied, only 1 case was negative for both of them. In this case, CD56 was helpful in confirming the diagnosis. Synaptophysin was positive in 60(96.8%) patients which was the majority of the NET of G1 & G2 WDNET. There were 8(100%)cases of G3 WDNET and 12(92.3%) of NEC.

Chromogranin also had a similar pattern of positivity in 49(94.2%) of G1 and G2 WDNET, and G3 WDNET was seen in 5(83.3%) and 5(45.4%) of NEC.

Discussion

Neuroendocrine tumours are rare malignancies whose behaviour is dependent on the level of differentiation, proliferative indices and extent of invasion. Therefore, segregation of WDNET category from NEC not only imparts prognostic stratification but also ascertains therapeutic decision.[12] Utilizing special techniques like molecular analysis and immunohistochemistry aids in this division but morphological features have a major implication.[13,14]

The mean age at diagnosis for patients of GEP-NET was 52.2±16.4 years with 6th decade of life (27.1%) as the most common age group noted. Males (55.1%) have a slightly higher frequency of involvement than females (44.9%). The regional studies in different countries of Asia have similar peak age group at diagnosis. A nationwide retrospective analysis of GEP-NETs in China showed 50-60 years as peak age group with a male to female ratio of 1.4:1.[15] Joseph et al also found 41-60 year as the most commonly involved age range for GEP-NET in the Indian population. However, their male to female ratio was 2.7:1, slightly higher when compared to the Pakistani population (1.2:1).[16] Asian population is generally noted to have a younger age at diagnosis compared to Americans (53.0 years vs 63.0 years).[17]

Most (83.1%) of the patients diagnosed with GEP-NETs were symptomatic unlike those reported by Lim et al who had 73.4% patients asymptomatic.[18] The 8 patients frequently had complaints related to tumour mass effect in the form of abdominal pain, discomfort and a palpable abdominal mass. Only 19(16.9%) patients did not have symptoms related to neuroendocrine tumour and they were discovered accidently either on routine examination or excision biopsy done for some other disease. The predominant site for these asymptomatic tumours was appendix (n= 11) followed by duodenum (n = 3).

Out of total 118 cases, 6(5.1%) tumours were functional that included 4 insulinomas and 2 gastrinomas, with 5 of them having their primaries in the pancreas. This compares with a study done in a local population of Turkey where retrospective analysis of 42 cases of GEP-NETs showed 4.8% functional NET.[19]

A significant load of GEP-NET was noted in the pancreas (28%) followed by the stomach (14.4%) as shown in table 1. The primary location of GEP-NETs has shown a diverse regional variability. A single centre study from Korea found duodenum as the most common primary

location, whereas pancreas and rectum were the most frequent primary location observed in China.[15,18,20] Buyukasik et al reported stomach as the most common site in his research in a hospital of Turkey.[19] Also published data from western countries have frequently shown small intestine as the most common primary site.[18,21]

The most frequent histological type was WDNET in 81.4% of the cases, followed by NEC in 16.0% (Table 2). Wang et al reported WDNET in 70.3% of the cases; however, NEC constituted 29.0%, which is higher than our population. It could be due to the reason that all grade 3 tumours (grade 3 WDNET and NEC) were included in this category. Manec had 0.7% in his study, slightly lower as compared to our population (2.5%).[22]

With the modification in WHO grading of GEP-NET more and more researches are now focusing on grade 3 WDNET. Although there is sufficient data available on neuroendocrine tumours but studies quoting grade III WDNET are limited. They have usually been reported in the range of 9-16% in literature.[20] We found 8.5% grade 3 WDNET, which is slightly lower than that reported. An Italian multicentre retrospective study identified 17.6% of the cases previously diagnosed as NEC, as WDNET grade 3 and majority of them were located in the pancreas,[22] while a single institutional experience in India showed 12.5% grade 3 WDNET.[23] However, researchers who have studied both NET and NEC have reported more grade 3 WDNET compared to NEC unlike our data (9.3% versus 16.9%).[22]

Grade 1 and 2 WDNET were predominantly seen in the pancreas (n=26) while grade 3 WDNET was more common in the colon (n=4), however, they were also seen in the stomach (n= 2), pancreas (n=2), duodenum (n=1) and oesophagus (n=1). Pancreas was also the most frequently involved site for NEC-unclassified (n=5) and LCNEC.[24,25] Low grade WDNET has commonly been reported in appendix, stomach and duodenum, while pancreas is a site common for grade 3 tumours as reported by various studies.[19,26] Whereas our observed data of Pakistan signifies that although pancreas is a common site for both low and high grade NET, but grade 3 WDNET have been found to be associated with colon more frequently.

Metastatic disease was evident in 15.3% cases at the time of diagnosis, which increased with the grade of the tumour (11.9% of low grade, 20% of grade 3 WDNET and 21% of NEC). The most common metastatic site was liver (11.9%) and 4 cases metastasized to abdominal wall (n=3) and lung (n=1). Pancreas (36.3%) was the most frequent primary site of tumour that showed distant metastasis. Lim et al have reported 8.9% GEP-NET with distant metastasis with liver as the most common site.[18] However, Yao et al have reported a much higher percentage of NET with metastatic disease. According to him, 21% of G1, 30% of G2 and 50% of poorly differentiated (G3) tumours or undifferentiated (G4) tumours had synchronous distant metastasis at diagnosis, which is much higher in comparison to Pakistani population.[26] Only 5% patients showed synchronous tumours that included 4 adenocarcinomas of stomach and 2 hepatocellular carcinoma. Kamp et al studied 459 GEP-NETs and found 2.8% had a synchronous tumour.[27]

A high positivity of synaptophysin was noted in all grades of GEP-NET. Chromogranin positivity however decreased with grade and differentiation of the tumour. This is in comparison to a study reported by Buyukasik et al, who found chromogranin A and synaptophysin positivity in 78.8% and 90.3% of gastroenteropancreatic NET, respectively, regardless of the grade 19. Wang et al studied chromogranin expression on 145 GEP-NET and they found 66% positivity in NET and 78% in NEC.[22]

Conclusion

GPNET has been found at various anatomic locations in gastrointestinal tract and pancreas with a wide variety of clinical presentation. Pancreas is the most commonly involved site by low as well as high grade NET tumours, while grade 3 WDNET had a predilection for colon.

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Conflict of Interest: None.

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