Clinicopathological features of gastroenteropancreatic neuroendocrine tumors: A retrospective evaluation of 42 cases

Kenan Büyükaşık1, Aziz Arı1, Cihad Tatar1, Bülent Akçe1, Mert Mahsunı Sevinç1, Serkan Sarı1, Esra Paşaoğlu2, Hasan Bektas1

ABSTRACT

Objective: Neuroendocrine tumors arise from neuroendocrine cells in any part of the body; approximately two thirds of these tumors are located in the gastrointestinal tract and pancreas. Although gastroenteropancreatic neuroendocrine tumors are known as rare neoplasms, their prevalence has recently increased due to advanced diagnostic methods and increased awareness of the disorder. In the present study, we aimed to review patients who were treated and followed up for gastroenteropancreatic neuroendocrine tumors at our clinic in terms of clinical picture, pathological findings, and prognosis.

Material and Methods: Data from 42 patients diagnosed with gastroenteropancreatic neuroendocrine tumors who were treated and followed up at our Training and Research Hospital from August 2011 to December 2015 were retrospectively evaluated.

Results: A total of 42 patients aged 17-81 years (mean age 46.9 years) were enrolled in the study. The most common symptom was abdominal pain, which was seen in 31 (73.8%) patients. Gastroenteropancreatic neuroendocrine tumors were detected in the stomach (n=5, 35.7%), appendix (n=11, 26.2%), rectum (n=6, 14.3%), pancreas (n=4, 9.5%), ileum and colon (n=2, 4.8%), and duodenum and jejunum (n=1, 2.4%). Local excision was performed in seven (16.7%) patients. Nine (21.4%) patients underwent gastric wedge resections, either by a laparoscopic procedure (n=3) or by open surgery (n=6). Total gastrectomy and laparoscopic subtotal gastrectomy were performed on three (7.1%) patients and two patients (4.8%), respectively. After the surgical procedures, the patients were followed up for a mean period of 36 months (15-57 months); the one-year and three-year survival rates were determined to be 100% and 97.6%, respectively.

Conclusion: Management of gastroenteropancreatic neuroendocrine tumors requires accumulation of knowledge and experience to establish a standardized approach. Therefore, we believe that collecting regular national data from these cases in every country will contribute to understanding the details of this entity worldwide.

Keywords: Chromogranin A, endoscopy, gastroenteropancreatic neuroendocrine tumor, ki-67 antigen, mitosis, synaptophysin

INTRODUCTION

Neuroendocrine tumors (NETs) arise from neuroendocrine cells in any part of the body; approximately two thirds of these tumors are located in the gastrointestinal tract and pancreas (1, 2). Although gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are known as rare neoplasms, their prevalence has recently increased due to advanced diagnostic methods and increased awareness of the disorder (3). The incidence of GEP-NETs was reported to be 3.65/100,000 according to the Surveillance, Epidemiology, and End Results database program (4). Because NETs may be located in various parts of the body and secrete different hormones, clinical findings may show differences with regard to mass effects on surrounding structures and the types of hormones secreted. However, most NETs are nonfunctional and present with non-specific symptoms such as abdominal pain and gastrointestinal bleeding.

According to the World Health Organization (WHO) 2010 classification (Table 1), GEP-NETs are classified as NET Grade 1 (G1) and NET Grade 2 (G2) (well-differentiated endocrine tumors in the WHO 2000 classification) and NEC Grade 3 (G3) (poorly differentiated endocrine carcinoma in the WHO 2000 classification) (5, 6). The WHO 2010 classification takes into account the mitotic rate (usually expressed as mitoses per 10 high power microscopic fields or per 2 mm) and/or Ki67 index (the percentage of neoplastic cells immunolabeled for the proliferation marker Ki67) when grading GEP-NETs. Tumors with a Ki67 index of <2% or a mitotic rate of <2/10 hpf are classified as G1, those with a Ki67 index of 3%-20% or a mitotic rate of 2-10/10 hpf are classified as G2, and those with a Ki67 index of >20% or a mitotic rate of >20/10 hpf are classified as G3 (7, 8).

In the present study, patients who were treated and followed up for GEP-NET at our clinic were reviewed in terms of clinical picture, pathological findings, and prognosis.
Table 1. WHO 2010 classification of GEP-NETs

| Grade          | Equivalent staging in WHO 2000 classification | Ki 67 index | Mitotic rate |
|----------------|-----------------------------------------------|-------------|--------------|
| NET Grade 1    | Well-differentiated endocrine tumors           | <2%         | <2/10 hpf    |
| NET Grade 2    |                                                | 3-20%       | 2-10/10 hpf  |
| NEC Grade 3    | Poorly differentiated endocrine carcinoma      | >20%        | >20/10 hpf   |

WHO: World Health Organization; GEP-NETS: gastroenteropancreatic neuroendocrine tumors; NET: neuroendocrine tumor

MATERIAL AND METHODS

Data from 42 patients diagnosed with GEP-NET who were treated and followed up at our Training and Research Hospital from August 2011 to December 2015 were retrospectively evaluated. We excluded patients from whom we did not obtain sufficient data, who could not be followed up, or who refused to participate in the study. The variables of age, gender, symptoms and signs, diagnostic methods, pathological findings, tumor features with regard to the WHO 2010 classification for GEP-NETS and the TNM staging system, and treatment and follow-up outcomes were recorded. The WHO 2010 classification for GEP-NETS was used as the grading system. Cancer staging was performed according to the TNM staging system for the involved organ or anatomical region for each tumor.

This research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects". Written informed consent was obtained from the patients who participated in this study.

RESULTS

A total of 42 patients (20 male, 22 female) aged 17-81 years (mean age 46.9 years) were enrolled in the study. The most common symptom was abdominal pain, which was seen in 31 (73.8%) patients. While two (4.3%) patients presented with hypoglycemic attack, one (2.4%) patient presented to the emergency department with blood in their vomit. One patient described recent constipation, while two patients presented to our outpatient clinic with weight loss and abdominal mass, respectively. While insulinoma was determined in two patients, the remaining patients (n=40, 95.2%) were determined to have hormonally nonfunctional GEP-NETS. Diagnosis was mostly made by endoscopy among the various diagnostic procedures used. Half the patients (n=21) were diagnosed through endoscopy, and endoscopic ultrasonography (EUS) was used in two patients. Computed tomography (CT) was performed on 13 (31%) patients. Eight (61.5%) of those provided a diagnosis of NET, while five (38.5%) had no diagnostic yield. Nine (21.4%) patients underwent positron emission tomography CT (PET-CT); there were no findings in two of those patients.

Gastroenteropancreatic neuroendocrine tumors were detected in the stomach (n=15, 35.7%), appendix (n=11, 26.2%), rectum (n=6, 14.3%), pancreas (n=4, 9.5%), ileum and colon (n=2, 4.8%), and duodenum and jejunum (n=1, 2.4%). A local excision was performed in seven (16.7%) patients. Nine (21.4%) patients underwent gastric wedge resections, either by a laparoscopic procedure (n=3) or by open surgery (n=6). Total gastrectomy and laparoscopic subtotal gastrectomy were performed in three (7.1%) patients and two patients (4.8%), respectively. Diagnosis of 11 (26.2%) patients was made after pathological examination of appendectomy specimens; therefore, their treatments were recorded as appendectomy. Distal pancreatectomy was performed in four (9.5%) patients, segmental ileal resection in two (4.8%) patients, low anterior resection in one (2.4%) patient, and segmental jejunal resection in one (2.4%) patient. Two patients were assumed to be inoperable due to distant metastases; therefore, they did not undergo surgery.

A range of tumor sizes between 2 and 105 mm was detected (mean size 9.7 mm) according to the pathology reports. Twenty-six (61.9%) patients presented with stage 1, 12 (28.6%) patients with stage 2, 2 (4.8%) patients with stage 3, and 2 (4.8%) patients with stage 4 tumors based on the TNM staging system. Ki-67 indices ≤2% were detected in 28 (66.7%) patients, between 2% and 20% in 13 (31%) patients, and >20% in 1 patient. Thirty-eight (90.5%) patients had a mitotic rate of <2/10, and 4 (9.5%) patients had a mitotic rate of 3 to 20/10. Twenty-eight (66.6%) patients were classified as NET G1, 13 (30.95%) were NET G2, and 1 (2.38%) was NEC G3 according to the WHO 2010 classification.

Staining for chromogranin A, for synaptophysin, and for neuron-specific enolase was positive in 26 (78.8%), 28 (90.3%), and 3 (7.1%) patients, respectively. Both chromogranin A and synaptophysin were found to be positive in one of two patients with metastasis; only synaptophysin was positive in the other patient in our study. These results are summarized in Table 2. After the surgical procedures, the patients were followed up for a mean period of 36 months (15-57 months); the one-year and three-year survival rates were determined to be 100% and 97.6%, respectively.

DISCUSSION

Neuroendocrine tumors are classified as functional and nonfunctional. Over 90% of patients are reported to have nonfunctional tumors (9); most nonfunctional GEP-NETS are found to present fairly late, with symptoms of mass effect or distant metastases (10). Functional GEP-NETS cause some symptoms due to excessive production of hormones or peptides. Various typical symptoms can be seen related to carcinoid syndrome, Zollinger-Ellison syndrome, Whipple’s triad, Verner-Morrison syndrome, insulinoma, and glucagonoma (11). However, Modlin et al. (12) advocated that categorizing these tumors as functional or nonfunctional is an archaic clinical concept because they are indistinguishable at the cellular, biological, and morphological levels.

Ninety-five per cent of NETs were determined to be nonfunctional in our study; the most common symptom was ab-
dominal pain, which was seen in three fourths of patients. The rate of distant metastasis was found to be less than 5%, and the pathological mean tumor size was measured as 9.7 mm. Therefore, although the prevalence of nonfunctional tumors is consistent with the literature, we cannot say this is true for the clinical picture because neither mass effect nor distant metastases were main features in the diagnosis of our cases. Zhang et al. (9) found that most patients (29.17%) presented with non-specific symptoms, such as abdominal or back pain. Neuroendocrine tumors are diagnosed and staged by CT, MRI, PET, US, endoscopy, and EUS. Functional imaging methods (somatostatin receptor scintigraphy, PET) are applicable because these tumors secrete hormones and peptides and express somatostatin receptors (13). The most accurate diagnostic method can differ according to tumor location. CT, MRI, and PET should be used for staging and follow-up of response to treatment according to the North American Neuroendocrine Tumor Society Guidelines (14). Our cases were mostly diagnosed through endoscopy. Though the other imaging methods were also used as diagnostic tools, they were mainly preferred for staging and follow-up. In addition, the GEP-NETs of 11 patients were incidentally detected by pathological examination of appendectomy specimens.

In two different studies, GEP-NETs were mostly located in the rectum (17.7%-58.93%), whereas the stomach (35.7%), appendix (26.2%), and rectum (14.3%) were the most frequently involved anatomic sites in our study. We consider that the distribution of GEP-NETs may differ between various countries (9, 15). A multidisciplinary approach is required in the treatment of GEP-NETs. It is advocated that surgery should be performed as a primary treatment as much as possible (16). It was reported that curative resections of primary tumor and locoregional lymph nodes provided 5-year and 10-year surv-

| Table 2. Clinicopathological features of the patients |
|-------------------------------------------------------|
| **Stomach** | **Duodenum** | **Jejunum** | **Ileum** | **Colon** | **Appendix** | **Rectum** | **Pancreas** | **Total** |
| n=15 | n=1 | n=1 | n=2 | n=2 | n=11 | n=6 | n=4 | n=42 |
| Stage (TNM) | | | | | | | | |
| Stage 1 | 6 | 1 | 1 | 1 | 2 | 10 | 3 | 2 | 26 |
| Stage 2 | 6 | - | - | - | - | 1 | 3 | 2 | 12 |
| Stage 3 | 1 | - | - | 1 | - | - | - | - | 2 |
| Stage 4 | 2 | - | - | - | - | - | - | - | 2 |
| Grade (WHO 2010) | | | | | | | | |
| G1 | 7 | 1 | 1 | 1 | 2 | 9 | 5 | 2 | 28 |
| G2 | 8 | - | - | 1 | - | 2 | 1 | 1 | 13 |
| G3 | - | - | - | - | - | - | - | 1 | 1 |
| Diagnosis | | | | | | | | |
| Endoscopy | 14 | 1 | - | - | 2 | - | 4 | - | - |
| EUS | 2 | - | - | - | - | - | - | - | - |
| CT | 1 | - | 1 | 2 | - | - | - | - | 4 |
| PET-CT | 3 | - | - | - | - | 2 | 2 | - | - |
| Incidental | - | - | - | - | - | - | - | 11 | - |
| Treatment | | | | | | | | |
| Laparoscopic gastric wedge resection | 3 | - | - | - | - | - | - | - | - |
| Open gastric wedge resection | 6 | - | - | - | - | - | - | - | - |
| Total gastrectomy | 3 | - | - | - | - | - | - | - | - |
| Laparoscopic subtotal gastrectomy | 2 | - | - | - | - | - | - | - | - |
| Appendectomy | - | - | - | - | - | - | - | - | 11 |
| Distal pancreatectomy | - | - | - | 2 | - | - | - | - | 4 |
| Segmental ileal resection | - | - | 1 | - | - | - | - | - | - |
| Segmental jejunal resection | - | - | - | - | - | - | - | - | - |
| Low anterior resection | - | - | - | - | - | - | - | 1 | - |
| Endoscopic local excision | - | 1 | - | - | - | 2 | - | 4 | - |
| Pathology | | | | | | | | |
| Chromogranin A | 10/11 | 1/1 | 1/1 | 2/2 | 1/2 | 5/6 | 3/6 | 3/4 | 26/33 |
| Synaptophysin | 10/11 | 1/1 | 1/1 | 2/2 | 1/2 | 5/5 | 5/5 | 3/4 | 28/31 |

WHO: World Health Organization; G: grade; EUS: endoscopic ultrasonography; CT: computed tomography; PET-CT: positron emission tomography-computed tomography
vival rates of 100% in stage 1 and 2 tumors and a 5-year survival rate of 95% and a 10-year survival rate of 80% in stage 3 tumors (17). The other therapeutic options are transcatheter arterial embolization, chemotherapy, somatostatin analogs, and novel therapies such as tyrosine kinase and angiogenesis inhibitors (9, 10).

We performed surgical procedures on almost all patients (95.2%). Only two (4.8%) patients were found to be unsuitable for surgery because one had an unresectable tumor and one presented with liver metastases. These patients were referred to the medical oncology clinic. The patient with an unresectable tumor died 28 months after diagnosis.

The WHO 2010 classification based on Ki-67 index and mitotic rate is currently used to grade GEP-NETs. In our series, 66.66% and 30.95% of patients were found to have G1 and G2 tumors, respectively. Although these tumors were assumed to be well-differentiated endocrine tumors in the WHO 2000 classification, NETs should be considered as potentially malignant lesions (18). The most commonly used immunohistochemical markers in pathological examination to identify NETs are chromogranin A and synaptophysin. Immunoreactivity of chromogranin A is more common in well-differentiated NETs, while that of synaptophysin is common in both well-differentiated NETs and poorly differentiated NECs (19, 20). In our study, positive immunohistochemical stainings for chromogranin A and synaptophysin were found with rates of 78.8% and 90.3%, respectively. Both these markers were found to be positive in one of two patients showing metastasis in our study; only synaptophysin was positive in the other patient.

The mean follow-up period was 36 months in our study, and the one-year and three-year survival rates were 100% and 97.6%, respectively. Wang et al. (21) reported 178 patients with a mean follow-up period of 8.6 years and with one-year, three-year, and five-year survival rates of 74.4%, 66.7%, and 54.5%, respectively. However, the mean tumor size in their study was larger than ours (3.9 cm versus 9.7 mm), and NEC G3 tumors were detected more frequently in their patients than in our study (30.2% versus 2.38%).

**CONCLUSION**

As a heterogeneous disorder, GEP-NETs can be located in various anatomic sites in the abdomen, resulting in a wide range of clinical pictures and requiring further awareness of relevant clinicians. A review of the literature revealed that management of GEP-NETs requires accumulation of knowledge and experience to establish a standardized approach. Therefore, we believe that collecting regular national data from these cases in every country will increase understanding of the details of this entity worldwide.

**Ethics Committee Approval:** Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki “Ethical Principles for Medical Research Involving Human Subjects” (amended in October 2013).

**Informed Consent** Written informed consent was obtained from patients who participated in this study.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept - K.B., C.T.; Design - K.B., C.T., A.A.; Supervision - B.A., M.M.S., S.S., H.B.; Resource - K.B., C.T., A.A., B.A.; Materials - K.B., C.T., A.A., B.A., M.M.S., E.P.; Data Collection and/or Processing - K.B., C.T., A.A., B.A., M.M.S., E.P.; Analysis and/or Interpretation - K.B., C.T., A.A., B.A., M.M.S.; Literature Search - K.B., C.T., A.A.; Writing Manuscript - K.B., C.T.; Critical Reviews - S.S., H.B.; Other - K.B., C.T., A.A., B.A., M.M.S., E.P., S.S., H.B.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study has received no financial support.

**REFERENCES**

1. Niederle MB, Hackl M, Kaserer K, Niederle B. Gastroenteropancreatic neuroendocrine euroidenocrine tumours: The current incidence and staging based on the WHO and European Neuroendocrine Tumour Society classification: An analysis based on prospectively collected parameters. Endocr Relat Cancer 2010; 17: 909-918. [CrossRef]

2. Serin KR, Keskin M, Gulluoglu M, Emre A. Atypical localisation of a gastrointestinal stromal tumour: a case report of pancreas gastrointestinal stromal tumour. Turk J Surg 2013; 29: 42-44. [CrossRef]

3. Modlin IM, Oberk G, Chung DC, Jensen RT, de Herder WW, Thakker RV. Gastroenteropancreatic neuroendocrine tumours. Lancet Oncol 2008; 9: 61-72. [CrossRef]

4. Lawrence B, Gustafsson BI, Chan A, Svejda B, Kidd M, Modlin IM. The epidemiology of gastroenteropancreatic neuroendocrine tumours. Endocrinol Metab Clin North Am 2011; 40: 1-18. [CrossRef]

5. Klöppel G. Classification and pathology of gastroenteropancreatic neuroendocrine neoplasms. Endocr Relat Cancer 2011; 18: 1-16. [CrossRef]

6. Bosman FT, Carneiro F, Hruban RH, Theise ND. WHO classification of tumours of the digestive system. Geneva, Switzerland: World Health Organization 2010.

7. Rindi G, Klöppel G, Altham H. TNM staging of foregut (neuroendocrine) tumours: a consensus proposal including a grading system. Virchows Arch 2006; 449: 395-401. [CrossRef]

8. Klímstra DS, Modlin IR, Coppola D, Lloyd RV, Suster S. The pathologic classification of neuroendocrine tumors: A review of nomenclature, grading, and staging systems. Pancreas 2010; 39: 707-712. [CrossRef]

9. Zhang X, Ma L, Bao H. Clinical, pathological and prognostic characteristics of gastroenteropancreatic neuroendocrine neoplasms in China: a retrospective study. BMC Endocr Disord 2014; 14: 54-56. [CrossRef]

10. Diez M, Teule A, Salazar R. Gastroenteropancreatic neuroendocrine tumours: diagnosis and treatment. Ann Gastroenterol 2013; 26: 29-36.

11. Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol 2008; 26: 3063-3072. [CrossRef]

12. Modlin IM, Moss SF, Gustafsson BI. The archaic distinction between functioning and nonfunctioning neuroendocrine neoplasms is no longer clinically relevant. Langenbecks Arch Surg 2011; 396: 1145-1156. [CrossRef]

13. Guven K, MRI, CT and FDG/PET/CT for diagnosis and follow-up of Gastroenteropancreatic Neuroendocrine tumours. Turk J Klinikeri J Med Oncol-Special Topics 2013; 6: 14-19.

14. Strosberg JRM, Coppola DM, Klímstra DS, Phan ATM, Kulke MHM, Wiseman GAM. The PANETS Consensus Guidelines for the Diagnosis and Management of Poorly Differentiated (High-Grade) Extrapulmonary Neuroendocrine Carcinomas. Pancreas 2010; 39: 799-780. [CrossRef]

15. Metz DC, Jensen RT. Gastrointestinal neuroendocrine tumors: pancreatic endocrine tumors. Gastroenterology 2008; 135: 1469-1492. [CrossRef]

16. Yanar H, Sivrikoz E, Yanar F. Local Surgical Treatment of Gastroenteropancreatic Neuroendocrine Tumors. Turk J Klinikeri J Med Oncol-Special Topics 2013; 6: 28-33.
17. Oberg K, Knigge U, Kwekkeboom D, Perren A. Neuroendocrine gastro-entero-pancreatic tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012; 23: 124-130. [CrossRef]

18. Chen C, Yi X, He Y. Gastroenteropancreatic neuroendocrine tumors (GEP-nets): a review. J Gastroint Dig Syst 2013; 3: 5-6.

19. Plöckinger U, Rindi G, Arnold R, Eriksson B, Krenning EP, de Herder WW. European Neuroendocrine Tumour Society. Guidelines for the diagnosis and treatment of neuroendocrine gastrointestinal tumours. A consensus statement on behalf of the European Neuroendocrine Tumour Society (ENETS). Neuroendocrinology 2004; 80: 394-424. [CrossRef]

20. Lloyd RV. Practical markers used in the diagnosis of neuroendocrine tumors. Endocr Pathol 2003; 14: 293-301. [CrossRef]

21. Wang YH, Lin Y, Xue L, Wang JH, Chen MH, Chen J. Relationship between clinical characteristics and survival of gastroenteropancreatic neuroendocrine neoplasms: A single-institution analysis (1995-2012) in South China. BMC Endocr Disord 2012; 12: 30-32. [CrossRef]