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Pathological characteristics and clinical specifications in gastroenteropancreatic neuroendocrine tumors: a study of 68 cases

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Abstract

Introduction: Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) represent a group of tumors, having their origin in cells of diffuse endocrine system, with particular clinical course, diagnosis and treatment. *Patients and Methods*: In our study, were included 68 patients with neuroendocrine digestive tumors admitted, diagnosed and treated in Fundeni Clinical Institute, Bucharest, in the last ten years – 2000–2010 (retrospective study). *Results*: Thirty-three (49%) patients were males, 35 (51%) females, and the main age was 58.9 years. In 62 (90.3%) cases was possible to find the primary tumor. The examined tumors had different localizations: pancreas – 32 (47.04%) cases (head – 17 (24.99%) cases, and body and tail – 15 (22.05%) cases), stomach – 7 (10.29%) cases, small intestine – 7 (10.29%) cases, 6 (8.82%) cases – unknown primary site (diagnosis was established on metastases), right colon – 6 (8.82%) cases, liver – 6 (8.82%) cases, rectum – 2 (2.94%) cases, and retroperitoneum – 2 (2.94%) cases. Microscopic examination revealed 59 (86.8%) malignant tumors and 9 (13.2%) benign tumors. Using *WHO 2000 Classification*, 28 cases of malignant tumors were well-differentiated neuroendocrine carcinomas, and 31 cases were poor differentiated neuroendocrine carcinomas. From malignant cases, 25 (42.3%) have distant metastases and 15 (25.9%) lymph node metastases. *Conclusions*: Cases of gastroenteropancreatic neuroendocrine tumors included in our study had clinical and histopathological features in correspondence with data from literature – slight predominance in women, predominance in 5th and 6th decades of life, the most frequent localizations were at pancreatic level – both head and body and tail, but the rarest were in colon and retroperitoneum. Most of the cases studied, were malignant tumors, from these more than a half were poor differentiated, and a quarter of them having lymph node or distant metastases.

Keywords: gastroenteropancreatic neuroendocrine tumors, pathological characteristics, clinical specifications.

Introduction

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) were representing, until not so far, a heterogeneous group of rare tumors (1% of all malignancies), having a particular clinical course and specific diagnosis and treatment. These tumors derived from diffuse endocrine system and were classified as APUD tumors, term that is not used these days. In *WHO 2000 Classification*, these tumors are named "neuroendocrine tumors". Nowadays, we noted an increasing incidence of these tumors (2–3/100 000 population per year), as the increasing of tumoral incidence in general. These tumors appear in general around sixth decade of life but may be found at any age [1–3].

The gastrointestinal mucosa and pancreas contains more than 15 different types of cells that are producing peptides and hormones that regulate gastrointestinal motility, digestion and metabolism, such as: chromogranin A and B, synaptophysin, gastrin, serotonin, insulin, glucagon, PP, ACTH, VIP, somatostatin, etc.

These cells, belonging to diffuse endocrine system, have some metabolic enzymes like neuron-specific enolase, and capacity to deposit amines and hormonal peptides in secretory vesicles. Most of the cells express glycoproteins like chromogranin and synaptophysin, and a high level of somatostatin surface receptors. The tumors that are developed from this tissue keep the capacity to express the mentioned products [4].

Gastrointestinal neuroendocrine tumors represent less than 2% of all gastrointestinal tumors. The most frequent site of these tumors is represented by appendix, followed by small bowel (ileum), rectum, stomach and colon. Gastric and ileal tumors are frequently multiple and the rest of them are in general solitary [5–8]. Pancreatic neuroendocrine tumors appear in 0.5–1.5% at autopsy but they are functional or symptomatic in less than 1/1000 cases resulting a 1/1 000 000 clinical detection rate which means 1–2% from all pancreatic neoplasms [9].

Also, the size of GEP-NETs may vary, as some tumors may be as small as 0.5 cm in diameters while other tumors may show a larger size of more than 10 cm in greatest dimension. At cut surface, they may show a tan color with a homogeneous surface while other tumors may show areas of hemorrhage and/or necrosis.

Grossly, GEP-NETs may have a nodular, fungated or infiltrative pattern, they may be well circumscribed, usually the benign counterparts, or have an invasive pattern of growth, mostly the malignant ones. Although malignant, the GEP-NETs are slow growing, but have a metastatic potential too, the highest metastatic potential being characteristic to ileal, gastric and colonic tumors versus appendicular and rectal tumors, that have a local extension [4, 7]. Microscopically, these tumors have mostly a nested or trabecular pattern with homogenous cellular features [1, 4, 7, 10]. Anyway, these tumors need a special attention, because of their frequent hormonal and peptide secretion, that may cause specific endocrine syndromes. Most of the tumors produce numerous peptides and hormones, but the clinical syndromes are determinate by the increased level of some specific hormones.

Patients and Methods

In our study were included 68 patients with digestive neuroendocrine tumors, admitted, diagnosed and treated in Fundeni Clinical Institute, Bucharest, between 2000–2010 (retrospective study). The cases were selected from a series of 500 patients from which were excluded cases of primary and metastatic malignant lymphomas, poor differentiated adenocarcinomas, squamous carcinomas and other types of poor differentiated tumors. The clinical data were collected from clinical files and histopathological data were collected from pathological registers. We have analyzed two types of features: clinical (tumor detection, gender and age of patients, functional status, etc.) and pathological features (tumor site, size, gross and microscopic appearance, presence of vascular and perineural invasion, presence of lymph node and distant metastases). In all 68 cases we have established the grade of differentiation, that were calculated using number of mitoses per 10 HPF for gastrointestinal NETs, and per 50 HPF – for pancreatic NETs, for G1 –<2 mitoses/10 HPF or <2 mitoses/50 HPF, respectively, for G2 – 2–20 mitoses/10 HPF or 2–50 mitoses/50 HPF, respectively, and for G3 >20 mitoses/10 HPF or >50 mitoses/50 HPF, respectively and stage (pTMN), using pTNM system for GEP-NETs [11, 12]. The study was based on surgical specimens – curative resections and removements of tumors (R0), the sampled fragments were fixed in 10% buffered formalin for 12–20 hours at room temperature (18–23^{0}C) and then were realized paraffin blocks, using standard histopathological protocol. The paraffin blocks were sectioned on rotary microtome at 2–3 μm and sections were collected on slides that were routinely stained with Hematoxylin–Eosin. The histopathological slides were examined and evaluated, separately, by two pathologists.

Histopathological typing of neuroendocrine tumors was made according to *WHO 2000 Classification* [13] as following:

- Well-differentiated endocrine tumor (WDET) benign or with unknown malignant potential;
- Well-differentiated endocrine carcinomas (WDEC) with low malignancy grade;
- Poor differentiated endocrine carcinomas (PDEC) with high malignancy grade.

At this time, we do not have data about the immunohistochemical markers in all cases. They could be performed only in few cases, but the results are inappropriate for conclusions.

Results

Assessment of clinical features

Tumor detection

In 62 (90.3%) cases was possible to detect a primary tumor *vs.* 6 (9.7%) cases in which this was not possible.

Gender distribution

Thirty-three (49%) of studied patients were males, and 35 (51%) were females.

Age distribution

The patients were distributed in age groups as followed: in groups of 10–19 years and ≥80 years – 2 (2.94%) cases each, in groups of 20–29 years and 30–39 years – 5 (7.35%) cases each, in group of 40–49 years – 7 (10.29%) cases, 11 (16.17%) cases in group of 70–79 years, 16 (23.52%) cases in group of 50–59 years and 20 (29.4%) cases in group of 60–69 years (Figure 1).

Functional status

Fourteen cases (20.5%) were functional, from these ten were localized in pancreas (insulinomas), two cases in stomach (gastrinomas) and two cases in duodenum (VIP-oma and gastrinoma).

Assessment of pathological features

Tumor site

The primary tumor was located as followed: 32 cases (47.04%) in pancreas – 17 (24.99%) cases in head and 15 (22.05%) cases in body and tail, stomach – 7 (10.29%) cases and small bowel – 7 (10.29%) cases, unknown primary site – 6 (8.82%) cases (diagnosis was established on metastases), right colon – 6 (8.82%) cases, liver – 6 (8.82%) cases, rectum – 2 (2.94%) cases and retroperitoneum – 2 (2.94%) cases (Figure 2).

Tumor gross aspects

The mean size of tumor in studied cases was 8.3 cm, varying between 0.5 and 20 cm. Grossly, most of the tumors, 57 (83.8%) cases, were white-grayish and only 11 (16.2%) cases were brown colored; in 19 (28.3%) cases the tumor has a nodular appearance, in 22 (32.8%) cases the tumor was fungated, in 24 (35.8%) cases – infiltrative, and in 2 (2.9%) cases – cystic (Figure 3).

Microscopic aspects

At the microscopic examination, 59 (86.8%) of the tumors were malignant and 9 (13.2%) were benign (WDET). According to *WHO 2000 Classification*, from malignant tumors, 28 cases were well-differentiated neuroendocrine carcinomas (WDEC) and 31 cases were poor differentiated neuroendocrine carcinomas (PDEC), (Figure 4); 25 (42.3%) carcinomas had distant metastases and 15 (25.9%) cases – lymph node metastases.

In two cases, there were tumoral vascular emboli and in one case, there was a perineural invasion.

Grading

Our cases were distributed as following: G1 – 29 (42.6%), G2 – 24 (35.3%), and G3 – 15 (22.1%). According to *WHO 2000 Classification*, the most of the studied cases were malignant – means neuroendocrine carcinomas, poor differentiated ones being less frequent than well-differentiated (Figures 5 and 6).

Staging

The cases, included in our study were TNM stadialized and clinical stages were with different from pathological ones in a small number of cases. The final staging was as following: stage I – 12 cases, stage IIa – 18 cases, stage IIb – 11 cases, stage IIIa – three cases, stage IIIb – seven cases, and stage IV – 17 cases.

Tumor associations

Three patients had synchronous colonic adenocarcinoma and other two patients – colonic tubular adenoma. One patient had a history of gastrointestinal stromal tumor and another patient had a history of pulmonary squamous carcinoma, both of them were treated appropriately.

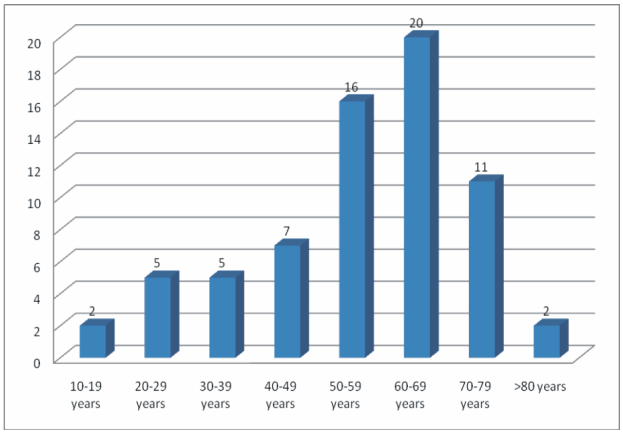

Figure 1 – ***Age distribution of studied NETs.***

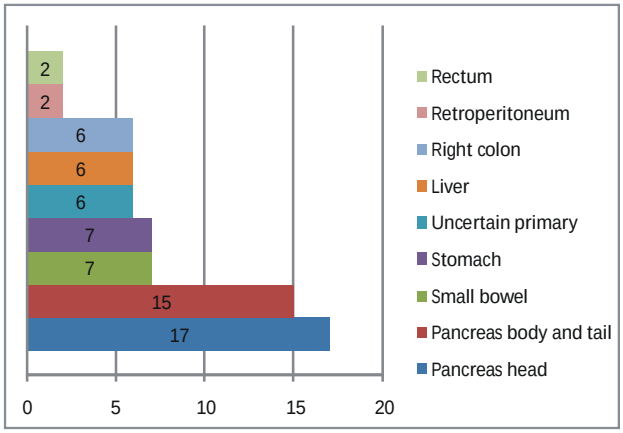

Figure 2 – ***Distribution of studied NETs by site of primary tumor.***

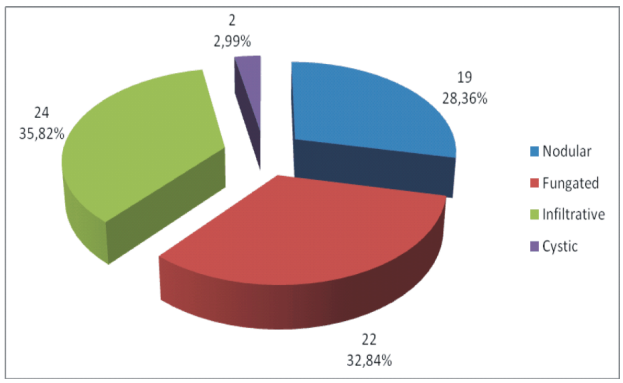

Figure 3 – ***Distribution of cases based on gross appearance.***

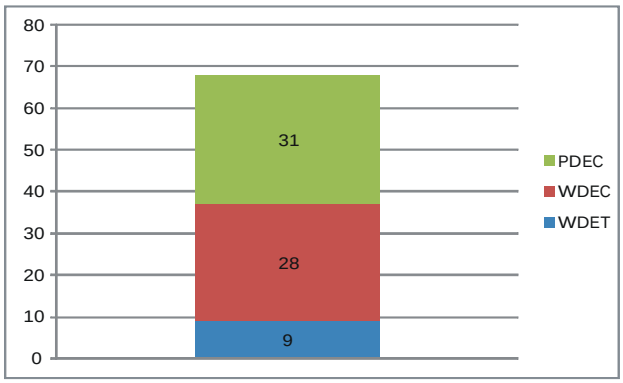

Figure 4 – ***Distribution of cases based on WHO 2000 Classification.***

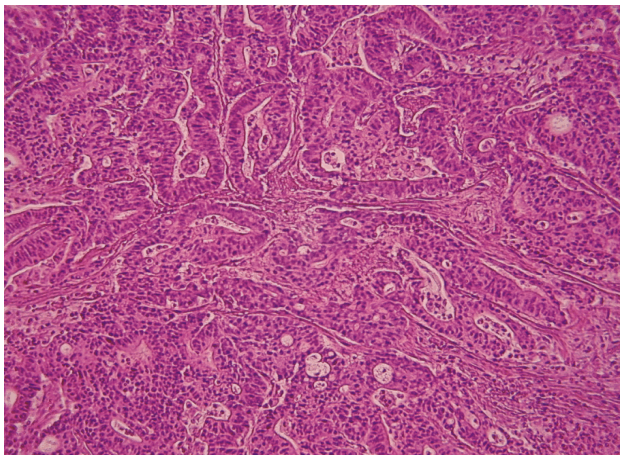

Figure 5 – ***Microscopic appearance of well-differentiated pancreatic endocrine neoplasm (HE stain, ×100).***

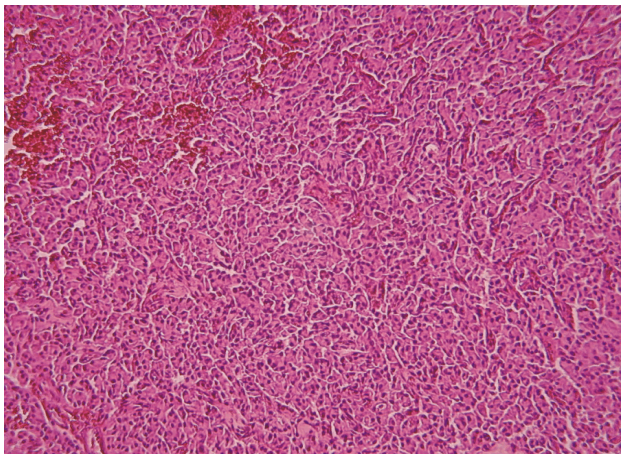

Figure 6 – ***Microscopic appearance of poor differentiated pancreatic endocrine neoplasm (HE stain, ×100).***

Discussion

Digestive neuroendocrine tumors are representing a much-studied issue in last years. According to literature, these tumors have a slight predominance in women – 2.4:2. In studied cases, we observed almost the same predominance. The digestive neuroendocrine tumors appear in general in 6th decade of life but they may be founded in any age, data obtained in studies from United States – 169 patients, and Switzerland – 433 patients [1, 2, 13, 14]. In our study the most frequent patients were included in groups of age around 6th decade too; in most of the patients (92%) it was possible to detect a primary tumor, but in rest of the cases, the site of this remain unknown. In literature, the unknown sites of primary tumor founded in 2 to 35% [14–16]. However, in most of these cases, the primary tumor may be located in small intestine or appendix, having a very small (millimetric) size, and it is very difficult to be diagnosed by usual techniques.

About site of primary tumor, according to literature, the most frequent digestive neuroendocrine tumors are localized in small intestine, in particular ileon – 25%, then in appendix and rectum – 20% each, and in stomach – 2–4% only [1, 10, 16,17,18].

Pancreatic neuroendocrine tumors appear in 0.5–1.5% at autopsy but they are functional or symptomatic in less than 1/1000 cases resulting a 1/1 000 000 clinical detection rate which means 1–2% from all pancreatic neoplasms [9].

In some studies, non-functional pancreatic neuroendocrine tumors, insulinomas and gastrinomas have an equal frequency, nonetheless in a study of 29 cases from Switzerland, non-functional pancreatic neuroendocrine tumors are described to be twice more frequent [9, 19, 20]. In our study, most of the cases were located in pancreas, both head and body and tail, being followed by small intestine and stomach; we have no appendicular localizations.

The site of primary tumor in case of gastroenteropancreatic neuroendocrine tumors was described in literature as a prognostic factor. A number of authors showed that pancreatic localization of primary tumor represents a risk factor for decrease of survival rate [19, 20] but there is a study on 156 patients from Italy that did not observe the same correlation [19]. Anyway, the difference of survival rate at 5 and 10 years in pancreatic and ileal NET is not significant, one observed that there is a tendency to decrease of survival rate in pancreatic tumors.

Gross appearance of studied tumors was almost evenly distributed between nodular, fungated and infiltrative aspects, with rare cystic tumors, according to literature data, but gross features are not specific and only histopathological aspects have a diagnostic importance. We could follow the survival only in 48 (70%) of cases, because in 30% of cases we lost the following. After five years, survived 36 (75%) followed patients, all the remained patients with IVth stage (11 patients) and one patient with IIIb stage died.

Intense study of neuroendocrine tumors in the last period made possible to elaborate a classifications, diagnostic and prognostic criteria of these tumors. In our study, we used a *WHO 2000 Classification* that was presented above, in which term "carcinoid", used in *WHO 1980 Classification*, were replaced with terms: well-differentiated endocrine tumor (WDET), well-differentiated endocrine carcinoma (WDEC) and poor differentiated endocrine carcinoma (PDEC) [13]. According to *WHO 2000 Classification*, the most of the studied cases were malignant – means neuroendocrine carcinomas, poor differentiated ones being less frequent than well-differentiated (Figures 5 and 6). There is a therapeutic application of this classification, actual recommendations being chemotherapy for poor differentiated digestive neuroendocrine tumors and hormonal therapy – for well differentiated such tumors.

Gastroenteropancreatic neuroendocrine tumors may cause specific symptoms because of hormonal secretion. In these cases, the diagnoses are clinically based on hormonal levels, on imagistic methods of detection of primary tumor and metastases and on scintigraphy.

Anyway, the "gold standard" is represented by histopathological diagnosis, which can be made as frequently as possible [2, 17].

Conclusions

Cases of neuroendocrine digestive tumors included in our study had a clinical and histopathological features in correspondence with data from literature – slight predominance in women, predominance in 5th and 6th decades of life, the most frequent sites were at pancreatic level both head and body and tail, but the rarest were in colon and mesentery. Most of the cases we studied were malignant tumors and from these more than half were poor differentiated, a quarter of them having lymph node or distant metastases. Regarding these aspects, data from literature are controversial and there are fields that have to be explored further on.

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