Rezumat

Tumorile pancreatice neuroendocrine - serie de cazuri şi sinteză a literaturii

Introducere: Tumorile neuroendocrine (TNE) sunt un grup heterogen de tumori cu manifestări clinice diferite şi comportament biologic divers. Localizarea pancreatică este una dintre cele mai frecvente pentru tumorile neuroendocrine. Deşi sunt considerate tumori relativ rare, studii mai recente asupra epidemiologiei TNE au demonstrat o incidenţă şi o prevalenţă crescândă în ultimii 30 de ani.

Scop: Am încercat să comparăm strategia terapeutică într-un mediu clinic real şi modelul ideal din literatură.

Materiale şi Metode: Seria noastră de cazuri constă în 18 pacienţi diagnosticaţi cu tumori pancreatice neuroendocrine pe o perioadă de 10 ani (2009-2018) internaţi şi trataţi în secţia Chirurgie I a Spitalului Clinic Dr. I. Cantacuzino. Cazurile au fost analizate retrospectiv privind particularităţile de diagnostic şi alegerea tratamentului urmată de prezentarea datelor din literatură.

Rezultate: Dintre cele 18 cazuri 13 au avut tumori funcţionale (11 insulinoame şi 2 gastrinoame), iar 5 tumori nefuncţionale. Majoritatea tumorilor au fost localizate în coada pancreasului (12 cazuri), celelalte au fost localizate în corp (1 caz) şi în capul pancreasului (5 cazuri). Tratamentul chirurgical a constat în 10 enucleări (dintre care 3 pe cale laparoscoplc) şi 8 rezeckii pancreatice, 2 dintre ele asociate cu splenectomie şi, într-un caz, a fost efectuată şi o metastazectomie hepatică. Urmărirea medie a fost de 12 luni. Nu s-au înregistrat recurenţe locale sau la distanţă.
cu o singură excepție, o femeie care s-a prezentat după un an cu o tumoră cefalo-pancreatică care s-a dovedit a fi un adenocarcinom.

Concluzii: Diagnosticul TNEP poate fi dificil chiar și în prezența unui sindrom de hipersecreție hormonală. Imagistica nucleară cu octreotid este utilă atât pentru localizarea tumorii și, de asemenea, cât și pentru a detecta eventuale tumori oculte care nu au fost evidențiate de explorările convensionale. Toate tumorile neuroendocrine pancreaticice ar trebui considerate potențial maligne și ar trebui evitată în mod special utilizarea termenului „benign”, de aceea gradul de diferențiere al tumorii trebuie stabilit pe baza numărului mitotic și a indicelui Ki-67. Tratamentul chirurgical rămâne singurul cu potențial curativ.

Cuvinte cheie: tumori pancreaticice neuroendocrine, insulinom, tumori neuroendocrine nefuncționale

Abstract

Background: Neuroendocrine tumors (NETs) are a heterogeneous group of tumors with various clinical manifestations and biological behavior. Among the most common neuroendocrine tumors (NETs) are pancreatic neuroendocrine tumors (PNETs). They are considered to be relatively rare tumors; however, more recent studies on NET epidemiology have demonstrated an increasing incidence and prevalence over the past 30 years.

Aims: We intend to compare the strategy used in a real life clinical environment in the case of pancreatic neuroendocrine tumors, as opposed to an ideal model, as presented in literature.

Materials and methods: Our case series consist in 18 patients with neuroendocrine pancreatic tumors diagnosed and treated in the Surgery I department of Clinical Hospital Dr. I. Cantacuzino over a 10-year period (2009-2018). We made a retrospective analysis of these patients, of their diagnosis particularities and choice of treatment and a review of the literature.

Results: Out of these 18 cases, 13 had functioning tumors (11 insulinomas and 2 gastrinomas) and 5 non-functioning tumors. Most of the tumors were located in the tail of the pancreas (12 cases) the others were located in the body (1 cases) and the head of the pancreas (5, cases). Surgical treatment consisted in 10 enucleations (3 of them laparoscopic) and 8 pancreatic resections, 2 of them associated with splenectomy and in one case a liver metastasectomy was also performed. The mean follow-up was 12 months. No local or distant recurrences were found with one exception, one female which presented after one year with a cephalic pancreatic tumor that proved to be an adenocarcinoma.

Conclusions: Diagnosis of PNETs may be difficult even in the presence of a hormonal hypersecretion syndrome. Nuclear imaging with octreotide is useful for locating the tumor and also for the detection of any possible occult tumors which cannot be identified through the use of conventional imaging. All PNETs should be considered as potentially malignant, and the use of the term “benign” should be particularly avoided, which is why tumor grading based on the mitotic count and Ki-67 index must be established for every case. Surgical treatment remains the only with curative potential

Key words: pancreatic neuroendocrine tumors, insulinoma, non-functioning neuroendocrine tumors
Introduction

Neuroendocrine tumors (NETs) are a heterogeneous group of tumors with various clinical manifestations and biological behavior. Among the most common neuroendocrine tumors (NETs) are pancreatic neuroendocrine tumors (PNETs) (1). Functioning PNETs produce specific hormonal hypersecretion syndromes. These include: insulinoma, gastrinoma, VIPoma, glucagonoma, and others types of rare tumors like PPoma, adrenocorticotropic hormone (ACTH)oma, growth hormone releasing factor (GRF)oma. However, the majority of PNETs do not produce these syndromes and are therefore classified as non-functioning. Morbidity and mortality are a direct product of their capacity of local invasion and distant spreading (2). Even if they are considered to be relatively rare tumors, more recent studies on NET epidemiology have demonstrated an increasing incidence and prevalence over the past 30 years (3). The majority of PNETs are moderately malignant but they can display a highly variable behavior from nearly benign to extremely aggressive (4). Therapy mainstays for pancreas neuroendocrine neoplasms include surgery and the use of somatostatin analogues.

Material and Methods

Our case series consist in 18 patients with neuroendocrine pancreatic tumors diagnosed and treated in the Surgery I department of Clinical Hospital Dr. I. Cantacuzino over a 10-year period (2009-2018). We made a retrospective analysis of these patients of their diagnosis particularities and choice of treatment and a review of the existing data in the literature regarding the epidemiology, diagnosis, treatment and prognosis of pancreatic neuroendocrine tumors. We have to mention that another case series represented by 16 patients with pancreatic insulinoma from our clinic was published in 2005 (5).

Results

18 patients were identified with a mean of age 53 years (limits 28 to 69) and a sex ratio male/female of 1 to 1.5. Out of these 13 were functioning tumors (11 insulinomas and 2 gastrinomas) and 5 nonfunctioning tumors.

The diagnosis was established preoperatively for all the functional tumors and for 2 case out of 5 nonfunctional tumors. Diagnosis was based on symptoms, high levels of insulin or gastrin and imaging studies represented by CT, MRI or SPECT-CT which located the tumor. The 2 cases with non-functional NETs were diagnosed also by echo-endoscopic FNA. For the rest of 3 cases with non-functional tumors the initial diagnosis was based on CT or MRI, and the final neuroendocrine tumor diagnosis was established after histopathological examination. At the moment of the diagnosis 2 patients had MEN I syndrome and another one with gastrinoma had a liver metastasis.

The time from the symptoms onset to diagnosis was more than one year for 5 of the patients with insulinoma, all of them with many evaluations including psychiatric treatment. In one case of insulinoma and one with gastrinoma even if the diagnosis was suspected at the onset of symptoms, the tumor was identified only after several years with repeated CT or MRI.

Most of the tumors were located in the tail of the pancreas (12 cases) the others were located in the body (1 cases) and the head of the pancreas (5 cases). 13 patients had tumors of 1-2 cm (all with insulinoma, one with metastatic gastrinoma and one with a nonfunctioning PNET), in 4 cases tumors had 2 to 5 cm and in one case 11 cm.

Surgical treatment consisted of 10 enucleations (3 of them laparoscopic) and 8 distal pancreatic resections 2 of them associated with splenectomy and in one case a liver metastectomy was also performed. In the figures below are presented some resections and enucleation specimen (Fig. 1).

Postoperative complications were noted in 5 patients: one postoperative bleeding after a gastrinoma’s enucleation which required reintervention and 4 pancreatic fistulas: 2 after
enucleation of one tumor located in the head and one inside the body of the pancreas and the other 2 after distal pancreatic resections. All pancreatic fistulas were treated conservatively and didn’t required a reintervention. No deaths were registered. The mean follow-up was 12 months. No local or distant recurrences were found with one exception. One female with an insulinoma of the pancreatic tail was admitted after 8 months with jaundice. Endoscopic sphincterotomy and stent placement were performed followed by a CT scan that revealed a 1.5 cm tumor in the pancreatic head. Intraoperative a 5 cm tumor was found and a total duodeno-pancreatectomy was performed. Histopathological examination diagnosis was pancreatic adenocarcinoma.

**Discussions**

Neuroendocrine tumors are considered relatively rare accounting for 0.46% of gastrointestinal and bronchopulmonary malignancies, their most frequent localization being the pancreas. Reported incidence in the last decade was less than 1 per 100,000 persons per year in population-based studies from Europe and Asia. The incidence and prevalence of NETs are steadily rising in the last 15 years probably due to increased detection by highly sensitive imaging diagnosis methods. Even if in our series a slightly predominance of female was noted studies haven’t found a clear difference regarding sex and even when taking into account the patients’race, geographic area, or socioeconomic status (6).

The cellular origin of PNETs is still unclear. Even if the term islet cell tumor was often used to identify PNETs many of them tumors do not develop directly from islet cells. They are originating from APUD stem
cells, which are pluripotential neuroendocrine cells located within the ductal epithelium of the exocrine pancreas and elsewhere in the distal foregut (7,8)

PNETs are classified by their capacity to cause hormonal hypersecretion syndrome as functioning or non-functioning. If functioning PNETs result in hormonal hypersecretion syndromes (Table 1), non-functioning PNETs can be found incidentally on imaging studies or after the histopathological examination because they have no specific symptoms. The main way to differentiate between functioning and non-functioning PNETs is through the patient’s clinical presentation. Both functioning and non-functioning PNETs express hormones which show no absolute difference, when analyzed. Both types of hormones, those that are normally expressed by pancreatic islets (insulin, glucagon, somatostatin, and pancreatic polypeptide), and those which are not normally found in pancreatic islets (gastrin, vasoactive intestinal peptide, serotonin, adrenocorticotropin, corticotropin-releasing hormone, parathyroid hormone, growth hormone-releasing hormone, growth hormone, calcitonin) can be secreted by most PNETs, as evidenced by immunochemical examination (9). These hormones may be biologically inactive or not secreted per se by the tumor. These tumors can however shift their profile over time, changing from non-functioning to functioning, thus triggering a hormonal hypersecretion syndrome (10).

About 90% of PNETs occur as sporadic tumors and approximately 10% of the different functioning-PNETs occur as part of an inherited syndrome like MEN 1, von Hippel Lindau, von Recklinghausen’s syndrome (neurofibromatosis 1), and tuberous sclerosis (4,11,12). If in each of the latter inherited syndromes the patients rarely develop a functioning PNET, MEN1 remains the most important inherited condition responsible for 20–30% of gastrinoma, <5% of insulinomas or other rare types of functioning pancreatic neuroendocrine tumors (11-14).

The clinical diagnosis may be difficult and often delayed because the symptoms of non-functioning PNETs are nonspecific and the recognition of hormonal hypersecretion syndrome is not easy requiring considerable clinical experience. In our series the period from the onset of the symptoms to diagnosis was more than a year for all the functioning tumor. In two cases even if the clinical and biological syndrome was present, the localization of the tumor required repeated imaging studies and in one case, even an exploratory laparotomy.

To achieve a full diagnosis the PNET nature and tumor grade should be established, the primary tumor and any existing metastases should be identified, and also the tumor function should be determined. For these are required endocrine testing, imaging and histological evidence. Any incidentally identified pancreatic or liver masses should be biopsied and undergo a histopathological examination in order to confirm the possible NET diagnosis. In the presence of a hormonal hypersecretion syndrome biochemical testing is useful to evaluate the hypersecretion and followed after confirmation by imaging and biopsy (1).

Biochemical testing may be useful to identify subclinical stage of a hormonal hypersecretion. The hormones may also be used for follow-up evaluations as tumor markers. The hormones most commonly produced by the functioning PNETs are insulin, proinsulin, gastrin, glucagon, pancreatic polypeptide (PP) and vasoactive intestinal peptide (VIP) so

### Table 1. Functioning PNET syndromes

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Symptom(s)</th>
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<tbody>
<tr>
<td>Insulinoma</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>Gastrinoma</td>
<td>Severe peptic ulceration</td>
</tr>
<tr>
<td>Vipoma</td>
<td>Watery diarrhea, hypokalemia, achlorhydria (WDHA syndrome)</td>
</tr>
<tr>
<td>Glucagonoma</td>
<td>Glucose intolerance, necrolytic migratory, erythema, stomatitis/glossitis, hypoaminoacidemia</td>
</tr>
<tr>
<td>Somatostatinoma</td>
<td>Hyperglycemia, choledolithiasis, steatorrhea, achlorhydria</td>
</tr>
</tbody>
</table>
their levels should be measured during a fasting period.

The most useful PNET marker is Chromogranin A (CGA), followed closely by neuron-specific enolase (NSE), and pancreastatin (15,16). However, false positive results may arise in patients suffering from atrophic gastritis and habitual users of antacids, as they can exhibit higher than normal levels of CGA (17,18).

Imaging studies are necessary for locating and staging of the tumor. In order to gauge the spread of the tumor computed tomography (CT) or magnetic resonance imaging (MRI) are necessary (19,20). Nuclear imaging with octreotide is useful for establishing the tumor affinity for somatostatin and also for the detection of any possible occult tumors which cannot be identified through the use of conventional imaging, and it is recommended to be performed at least once (21,22). FDG-PET is useful only for highly aggressive tumors. Most PNETs are negative so that it is not usually indicated (23,24). An extremely sensitive method for detecting small tumors and extra-hepatic metastasis of PNETs is PET with gallium 68–labeled octreotide (25,26). Studies showed a sensitivity from 86–100%, and a specificity from 79–100% for all PNETs (27-29), with the exception of insulinomas, in which the sensitivity is only 25% (30). Has been shown that this method of detection can change the tumor management (staging, surgical or medical treatment) in 20–55% of patients (31,32) and therefore it should be performed in all patients with PNETs except insulinomas.

Various TNM classification systems with grading have been developed for neuroendocrine tumors as well as for PNETs: WHO2010 (World Health Organization), ENETs (European Neuroendocrine Tumor Society), AJCC (American Joint Committee on Cancer) These classifications are presented in Table 2 (33,34).

The grading systems are based on agreed cut-points of mitotic rate and Ki-67 proliferative index and split neuroendocrine tumors into low, intermediate or high grade. These grades are prognostically significant, showing decreased survival as grade increased (35). Studies has proven, for each of these classifications/grading systems, that they have prognostic value for patients with PNETs. Using of one of these classification/grading systems is now essential to select the correct treatment for patients and especially for those with aggressive or advanced disease (36).

Minimal Consensus Statement regarding high grade gastroentero-pancreatic neuroendocrine tumors from ENETS guidelines stated that a routine pathological report should include morphology (large cell vs. small cell and differentiation), staining for chromo-

<table>
<thead>
<tr>
<th>Mitosis</th>
<th>Ki-67%</th>
<th>ENETS/WHO</th>
<th>Grade</th>
</tr>
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<tbody>
<tr>
<td>&lt; 2</td>
<td>&lt; 3</td>
<td>NET</td>
<td>I</td>
</tr>
<tr>
<td>2–20</td>
<td>3–20</td>
<td>NET</td>
<td>II</td>
</tr>
<tr>
<td>&gt; 20</td>
<td>&gt; 20</td>
<td>NEC (small cell or large cells)</td>
<td>III</td>
</tr>
</tbody>
</table>

Mixed adenoendocrine carcinoma (MANEC)

<table>
<thead>
<tr>
<th>ENETS TNM</th>
<th>AJCC/UICC TNM</th>
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<tbody>
<tr>
<td>T1 Limited to pancreas, &lt; 2 cm</td>
<td>Limited to pancreas, &lt; 2 cm</td>
</tr>
<tr>
<td>T2 Limited to pancreas, 2–4 cm</td>
<td>Limited to pancreas, &gt; 2 cm</td>
</tr>
<tr>
<td>T3 Limited to pancreas &gt; 4 cm; or tumor invasion of duodenum or common bile duct</td>
<td>Tumor invasion of peripancreatic tissue. Not involving major vascular invasion (truncus coeliacus, A. mesenterica superior)</td>
</tr>
<tr>
<td>T4 Tumor invasion of any adjacent structure or involving major vascular invasion</td>
<td>Involving major vascular invasion</td>
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Table 2. Neuroendocrine tumors grading
In the last 10–20 years, a paradigm shift occurred regarding PNETs treatment strategy (37), from a “wait-and-see” to an “aggressive” approach. This shift is based on the assumption that patients will invariably benefit from a reduction of both the primary tumor and the metastases. The increasing popularity of this approach is also based on the increase in the safety in experienced centers. It has 4 components: surgery, locoregional therapy, systemic therapy, and complication control (38).

Surgical treatment can achieve: a clinical cure in the case of nonmetastatic tumors, a reduction of hormone secretion through the debulking of liver metastases of functioning PNETs, and also a decrease of the tumor mass effects for all PNET types (1). Surgery is recommended by all guidelines for the patients without life-limiting comorbidities or high surgical risk. Recommendations also stated that symptoms of hormonal excess should be treated with octreotide or lanreotide before surgery. Such treatment is contraindicated in patients with insulinoma because of the risk of lethal outcome (1).

If treatment with octreotide or lanreotide is planned, cholecystectomy is recommended during surgical resection, due to the increased rate of biliary problems associated with the long-term use of these agents (39).

For nonfunctioning PNETs the therapeutic approach depends on tumor localizations and size. For tumors ≤2 cm enucleation with strong consideration of lymph node resection or pancreatectomy (proximal or distal) with or without regional lymph node resection/splenectomy are indicated. For tumors > 2 cm, pancreatectomy with regional lymph node resection is indicated: Whipple-type or proximal pancreatectomy should be performed in those located in the pancreatic head and distal pancreatectomy with splenectomy for those located distally (40).

Locoregional therapy of unresectable liver metastases include: radiofrequency ablation (RFA), radioactive polymer microspheres, chemoembolization, bland embolization, transcutaneous alcohol ablation, and microwave ablation. These are indicated for most patients with unresectable liver metastases and all have been successfully used (41,42).

For patients with residual disease following surgery and locoregional therapy systemic therapy is a must. In functioning PNETs, especially for VIPoma and glucagonoma, somatostatin analogs are indicated (1). In cases with non-functioning PNETs there is no clear evidence that treatment with somatostatin analogs is effective, but they may restrain tumor growth (43). The somatostatin analogs used are octreotide and lanreotide. These are also available in a long-acting release form. Pasireotide, is a new analog that showed encouraging preliminary results in clinical trials (44). In all PNET cases with a tumor burden, somatostatin analog treatment is strongly recommended (especially considering the high benefit/risk ratio associated). Everolimus (the mTOR inhibitor) and sunitinib (the tyrosine kinase inhibitor) are another two compounds that studies have shown top-long progression-free survival by an average of 10 months in patients with well-differentiated PNETs; however, the best indication for these drugs needs further study. Chemotherapy remains reserved for intermediate and high-grade PNETs (45,46).

Common complications and side effects of PNET treatment include: hyperglycemia, malabsorption, various types vitamin deficiencies, and the increased likelihood of cerebral spinal and bone metastases. These complications can be treated by a combination of diet, pancreatic enzyme replacement, insulin necessary, or if the need should arise, external beam radiation therapy (47,48).

Even though the life expectancy of these patients may be significantly reduced when compared to the general population, their prognosis is still better than in the case of patients diagnosed with pancreatic adenocarcinomas. In the case of patients that survive past the 1 year or 5 year mark, life expectancy has a fairly high probability of...
being close to normal. It has long been recognized that the development, presence and extent of liver metastases are one of the most important prognostic factors in patients with p-NETs, however the role of lymph node metastases as a prognostic factor has remained controversial (49).

Conclusions

As shown in this study, the diagnosis may prove to be a lengthy and difficult process even in the presence of a hormonal hypersecretion syndrome. Nuclear imaging with octreotide is useful for locating the tumor and also for the detection of any possible occult tumors which cannot be identified through the use of conventional imaging. All PNETs should be considered as potentially malignant, and the use of the term “benign” should be particularly avoided, which is why tumor grading based on the mitotic count and Ki-67 index must be established for every case. Surgical treatment is the only with curative potential. It plays and important role even in advanced cases by debulking of liver PNET metastases and reducing the tumor burden.

Author’s Contributions

All authors contributed equally to the manuscript.

Conflict of Interest

The authors declare no conflicts of interests.

References

23. Adams S, Baum R, Rink T, Schumm-Dräger PM, Usadel KH, Höf G.


