Diagnosis and Management of Neuroendocrine Tumors

Definitions and Terminology

Endocrine tumors of the digestive system are rare events and present with widely variable and often dramatic clinical syndromes. Several synonyms are currently used by clinicians and pathologists for these tumors, including "carcinoid tumor," "APUD-oma," "gastro-entero-pancreatic (GEP) tumor," "islet cell tumor," "neuroendocrine tumor," and "neuroendocrine carcinoma." The term "carcinoid" was introduced in 1902 by Oberndorfer[1] for malignant tumors arising in the small intestine that formed metastases but differed from other malignancies by a slow tumor growth. The terminology was confined to endocrine tumors of the esophagus, stomach, small and large intestine, and of organs developing from the digestive tract (such as the bronchial system).

Pancreatic endocrine tumors, despite revealing histologically many similarities with carcinoids, were excluded from this classification because of the different organogenesis of the pancreas. Recent consensus meetings suggested that the more appropriate term "neuroendocrine tumor" be used for all endocrine tumors of the digestive system, because all such tumors derive from the diffuse neuroendocrine system.[2,3] To this system belong: (a) the pancreas; (b) the mucosa of the gastrointestinal tract containing at least 15 different endocrine cell types producing hormonal peptides and/or biogenic amines[4,5]; and (c) endocrine cells scattered in other endodermal sites (such as the thyroid, lung, biliary tree, and the urogenital tract).

Neuroendocrine tumors can be subclassified into those with and those without a clinical syndrome and are accordingly termed "functionally active" and "functionally inactive" neuroendocrine tumors, respectively. Furthermore, neuroendocrine tumors can arise sporadically or as a result of genetic predisposition.

Pathophysiology

Functionally active neuroendocrine tumors present with clinical symptoms because of excessive hormone release from the tumor cell. Examples of such events are insulinoma, gastrinoma, VIPoma, glucagonoma syndrome, and carcinoid syndrome.
The excessive hormone release reflects the inability of the tumor cell to store newly synthesized hormone within the cell and to respond to a physiologically existing feedback mechanism that regulates hormone release. Within this context, insulin release from the beta cells of islets of Langerhans is dependent on circulating blood glucose levels, and ceases if the level decreases below 80 mg/dL. In insulinoma patients, tumor cells continue to release insulin despite decreasing blood glucose levels. Therefore, insulin levels in these patients are measurable in the setting of hypoglycemia, whereas they are not measurable during prolonged fasting in healthy subjects.

Functionally Inactive Tumors

Functionally inactive neuroendocrine tumors are diagnosed several ways: (1) by chance during routine ultrasonography performed for investigation of unexplained upper abdominal complaints; (2) in the case of large tumors of the pancreatic head, because of the consequent extrahepatic jaundice; (3) in the case of patients with relapsing abdominal cramps, as a result of intestinal pseudo-obstruction by a functionally inactive neuroendocrine tumor of the lower jejunum and ileum; or (4) as a result of tumor symptoms, such as gastrointestinal bleeding.

Genetics

Nonsporadic neuroendocrine tumors arise as a result of syndromes inherited in an autosomal dominant fashion for which the genetic pathways have recently been identified. These include: multiple endocrine neoplasia (MEN) types 1 and 2; von Hippel-Lindau (VHL) disease; von Recklinghausen’s neurofibromatosis (NF), and tuberculous sclerosis (TSC).[6] Exception for insulinoma, most neuroendocrine tumors are malignant, with metastases to lymph nodes and the liver (most common) or bone, lung, brain, and other organs (uncommon). Despite metastatic spread, most malignant neuroendocrine tumors grow slowly, reflecting the low mitotic activity of these largely well-differentiated tumors.

The management approaches for patients with neuroendocrine tumors have increased greatly in recent years and have included improvements in pathohistologic and biochemical diagnosis, tumor localization, and new treatment modalities for controlling hormone-mediated clinical syndromes and tumor growth.

During a symposium held at the 8th United European Gastroenterology Week, November 25-30, 2000 in Brussels, Belgium, leading authorities from throughout Europe discussed the impact of such recent improvements in diagnosis and treatment of these lesions. This report summarizes the key points highlighted in these proceedings.

Pathological Classification and Prognostic Factors

Classification

Professor G. Rindi, Chief of the Department of Pathology, University of Brescia, Italy, introduced a discussion on the classification of neuroendocrine tumors based on proceedings of the recent World Health Organization conference, which also included other leading pathologists.[7] According to this classification scheme, neuroendocrine tumors should be stratified into (1) well-differentiated neuroendocrine tumors and (2) poorly differentiated small-cell neuroendocrine carcinoma. Poorly differentiated tumors are rare, fast growing, and, therefore, highly malignant, resembling small-cell lung cancer.

Definition of Malignancy

Well-differentiated tumors are the more predominant form of neuroendocrine tumors of the digestive tract. They may be either benign or malignant. Malignancy of well-differentiated neuroendocrine tumors is ascertained if synchronous metastases and/or invasiveness are present.

In those instances in which there are no metastases, malignancy is suggested by the presence of
the following: tumor size (tumors > 2 cm are more aggressive); invasion into adjacent tissue; wall invasion beyond the submucosa; angioinvasion and invasion into perineural spaces; the presence of necroses and overt cell atypia; > 2 mitoses in 10 microscopic high-power fields; loss of chromogranin A immunoreactivity; argyrophilia; or hormone expression and nuclear p53 protein accumulation.

**Staining**

To make the diagnosis, pathologists currently immunostain for general neuroendocrine markers that identify the neuroendocrine "nature" of the tumor, as well as cell-specific markers that can identify their discrete cellular products (such as peptides or biogenic amines).[8]

General markers of well-differentiated tumors include: Cytosolic markers, such as neuron-specific enolase (NSE) and protein gene product 9.5

- Small vesicle-associated markers, such as synaptophysin, synapsin, and synaptotagmin
- Secretory granule-associated markers, such as chromogranin A and HISL-19

Cell-specific markers include hormones, such as insulin, gastrin, and glucagon, which identify a tumor as an insulinoma, gastrinoma, or glucagonoma, respectively. Poorly differentiated tumors do not express cell-specific markers but should be positive for some of the general markers indicated above.

**Prognostic Markers**

Whereas in general oncology tumor grading is important in predicting prognosis, such histologic tumor grading is difficult in the case of neuroendocrine tumors. The previously discussed markers for defining malignancy cannot be used as predictors of tumor malignancy or outcome in this setting. Recently, it has been shown that in malignant neuroendocrine tumors of the stomach, survival is negatively correlated with high Ki67 protein expression (> 2%) and the presence of aneuploidy.[9] The latest results presented by Professor Rindi's group[9] suggest that this is also true for other neuroendocrine carcinomas.

**Diagnostic Possibilities**

**Biochemical Markers**

Professor K. Öberg, Chief of the Section for Endocrine Oncology, Department of Medical Sciences, University Hospital, Uppsala, Sweden, summarized the diagnostic steps and stressed the clinical utility of biochemical parameters in the work-up.

If a neuroendocrine tumor is suggested by clinical symptoms (eg, as neuroglucopenia in insulinoma, relapsing ulcer diathesis, watery diarrhea, reflux disease in gastrinoma, flushing and diarrhea in carcinoid syndrome, necrolytic migratory erythema and diabetes mellitus in glucagonoma syndrome, watery diarrhea in Verner-Morrison syndrome), measurement of the related hormones is indicated.

Insulinoma causes fasting hypoglycemia because of inappropriate insulin secretion. The diagnosis of an insulinoma can be ascertained by demonstrating neuroglucopenic symptoms in the setting of hypoglycemia (blood glucose < 50 mg/dL) during prolonged, supervised fasting (up to 72 hours), in association with still measurable, but not elevated, blood insulin or C-peptide levels. The biochemical diagnosis of the other syndromes is based on the demonstration of elevated marker hormones (eg, gastrin) in the presence of ulcer diathesis, VIP (vasoactive intestinal peptide) in the presence of watery diarrhea, etc.

An important screening marker for neuroendocrine tumors is chromogranin A (CgA). In addition to specific peptide hormones, secretory granules of neuroendocrine cells contain 1 or more
chromogranin/secretogranin proteins.\textsuperscript{[10,11]} These peptides belong to a unique family of secretory proteins that share many biochemical properties and are exclusively localized in neuronal and neuroendocrine secretory granules.\textsuperscript{[12]} The first member of this family is CgA. Its name derives from the fact that it was originally identified in the catecholamine-containing chromaffin granules of the adrenal medulla.\textsuperscript{[13]}

The ubiquitous presence of CgA in neuroendocrine cells and its cosecretion with peptide hormones and neuropeptides make it a useful tissue and serum marker of tumors of neuroendocrine origin.\textsuperscript{[14]} Plasma levels of CgA are elevated in most neuroendocrine tumor syndromes and, most important, also in functionally inactive tumors. The highest levels have been reported in patients with metastatic carcinoid tumors arising from the midgut (i.e., from the jejunum and ileum). Patients with multiple and large liver metastases have higher CgA levels than patients with few metastases. Thus, CgA levels reflect tumor burden and high levels seem to predict shorter survival.\textsuperscript{[15]} False-positive elevation in CgA level has been reported in patients with atrophic gastritis, liver cirrhosis, and kidney failure.

**Imaging**

As a consequence of the lack of controlled studies, diagnostic strategies for imaging neuroendocrine tumors vary considerably among centers. Prior to the availability of somatostatin receptor scintigraphy (SRS), conventional noninvasive imaging modalities (ultrasound, CT scan, MRI, and bone scanning) as well as invasive imaging modalities (angiography, selective venous sampling for hormonal gradients) were widely used.

During the years 1998 and 1999, a group of experts within the European Network of Neuroendocrine Tumors (ENET), developed recommendations for imaging that reflect the clinician's experience relative to their field (radiology, nuclear medicine, gastroenterology, and surgery).\textsuperscript{[16]} Workflow charts have been elaborated for nonfunctional and functional endocrine tumors of the pancreas; insulinoma; enterochromaffin-like (ECL)-cell tumor of the stomach; assessment of unknown primaries in functional and nonfunctional neuroendocrine tumors of the gut; and assessment of metastases in functional and nonfunctional neuroendocrine tumors. In these workflow charts, SRS has gained a central role, whereas tomographic procedures such as CT and MRI serve for the completion of the oncologic work-up.\textsuperscript{[17,18]}

All available studies demonstrate that both SRS and endoscopic ultrasonography have a direct clinical impact because they influence individual therapeutic strategies.\textsuperscript{[19,20]}

**What Are the Therapeutic Possibilities?**

Because of the rarity of neuroendocrine tumors, only a few randomized, prospective, and controlled therapeutic trials have been published thus far. Unfortunately, in these trials, several tumor entities (e.g., tumors arising from the foregut [stomach, pancreas], midgut [jejunum, ileum, right colon], and hindgut [left colon]) have all been included.

This fact ignores the distinct and spontaneous growth behaviors and sensitivities to therapeutic agents that are demonstrated by neuroendocrine tumors of different origin. Therefore, the treatment of neuroendocrine tumors is rather empirical. The aim of treating these patients is control of the hormone-mediated symptoms and tumor growth. Whenever viable, curative surgical removal of the tumor should always be attempted. However, this is only possible for benign tumors (e.g., insulinasomas, which are indeed benign in more than 90% of cases) and for 30% to 50% of cases of sporadic gastrinoma.

**Medical Treatment**

Professor R. Arnold, Chief of the Department of Internal Medicine, Philipps University, Marburg, Germany, summarized the available data on long-acting somatostatin analogs, alfa-interferon, and chemotherapeutic drugs. He mentioned that surgical debulking should always be considered in palliative settings before initiation of any medical interventions to control tumor symptoms and tumor growth.
**Somatostatin analogs.** Somatostatin and its long-acting analogs have been proven to be the drugs of first choice for the reliable control of hormone-mediated symptoms. Octreotide and lanreotide have shown efficacy in the control of watery diarrhea for patients with Werner-Morrison syndrome (VIPoma), for control of necrolytic migratory erythema in patients with glucagonoma syndrome, and for management of flushing and diarrhea in patients with carcinoid syndrome.[21]

The newly developed long-acting, slow-release formulation of octreotide (which is administered once monthly intramuscularly as opposed to 3 times/day subcutaneously, as in the case of the standard formulation), has also been shown to control hormone-mediated symptoms effectively. Long-acting somatostatin analogs are less effective in the control of hypoglycemia in insulinoma patients because only 50% of insulinomas have somatostatin receptors. The control of gastric acid hypersecretion in gastrinoma is easier to achieve with oral proton-pump inhibitors (eg, omeprazole, lansoprazole, pantoprazole); however, the doses required for efficacy are higher than those required for control of "regular" ulcer disease.

Dr. Arnold also discussed the effect of long-acting somatostatin analogs in the control of tumor growth. Evidence for the antiproliferative properties of somatostatin and its analogs derives from in vitro and in vivo studies.[21] Available data indicate that the antiproliferative effects of somatostatin are mediated via somatostatin receptors and that somatostatin subtype-2 receptor (SSTR2) and SSTR5 are the most important in this setting. In addition, receptor-independent effects (eg, endocrine effects that interfere with tumor growth-promoting humoral factors, vascular effects with the inhibition of angiogenesis, and effects on the immune system) all contribute to the inhibition of growth. To date, 5 studies have been published that investigated the effect of long-acting somatostatin analogs in humans (see Table 1).[22-26]

**Table 1. Long-acting Somatostatin Analogues in the Control of Growth in Patients With Metastatic Neuroendocrine GEP Tumors**

<table>
<thead>
<tr>
<th></th>
<th>Regular dose</th>
<th>Ultrahigh dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saltz et al, 1993[22]</td>
<td>Stabilization of tumor growth for 2-27 months in 50%</td>
<td>Stabilization of tumor growth for 6-32 months in 70%</td>
</tr>
<tr>
<td>n = 34</td>
<td>No tumor regression</td>
<td>Partial tumor regression in 5%</td>
</tr>
<tr>
<td>Arnold et al, 1996[23]</td>
<td>Stabilization of tumor growth for 3-60 months in 36%</td>
<td>Stabilization of tumor growth after 1 year in 36%</td>
</tr>
<tr>
<td>n = 52</td>
<td>No tumor regression</td>
<td>Partial tumor regression in 3%</td>
</tr>
<tr>
<td>Di Bartolomeo et al, 1996[24]</td>
<td>Stabilization of tumor growth for 6-32 months in 52%</td>
<td>Complete remission in 3%</td>
</tr>
<tr>
<td>n = 38</td>
<td>Partial tumor regression in 3%</td>
<td></td>
</tr>
</tbody>
</table>

Reprinted with permission of the publisher (S. Karger AG, Basel, Switzerland), from Arnold R, Simon B, Wied M. Digestion. 2000;62(suppl 1):84-91 [Table 4, p 89].

The studies indicated above are all comparable, because only patients with CT-documented progressive disease were included. Contrary to earlier studies in which the criterion of progressive
disease was not provided and which had a much more favorable result (tumor disappearance or shrinkage),[27] for the studies listed in Table 1, partial tumor regression was a rare event, with stabilization of tumor growth -- the most favorable result -- occurring in 36% to 70% of patients. Even stable disease was a temporary event in these studies, reported to last between 2 and 60 months. According to the results of these studies, it is not possible to predict which patient will respond to octreotide treatment in terms of tumor growth inhibition.

**Alfa-interferon.** Alfa-interferon also exerts antiproliferative potency, as determined based on its effects on kidney malignancies and some forms of leukemia. This agent was introduced by Öberg and coworkers[28] to the treatment of neuroendocrine carcinomas in 1982 because of its ability to stimulate natural killer cell function and to control hormone secretion, clinical symptoms, and tumor growth. The various published trials with alfa-interferon are summarized in Table 2.

**Table 2. Alfa-Interferon Therapy in Patients With Neuroendocrine Tumors**

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Dose</th>
<th>Biochemical response, %</th>
<th>Tumor response, (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moertel et al</td>
<td>27</td>
<td>IFN(^{2a}) 24 MIU/m(^2) x 3/week SC</td>
<td>39</td>
<td>20</td>
</tr>
<tr>
<td>Schober et al</td>
<td>21</td>
<td>IFN(^{2b}) 3 MIU/m(^2) x 3/week SC</td>
<td>56</td>
<td>10</td>
</tr>
<tr>
<td>Hansen et al</td>
<td>19</td>
<td>IFN(^{2b}) 5 MIU x 8/week SC alone* or with embolization</td>
<td>40*; 86</td>
<td>10*, 86</td>
</tr>
<tr>
<td>Bartsch et al</td>
<td>18</td>
<td>rIFN(^{2c}) 2 MIU/m(^2) x 12/week SC</td>
<td>44</td>
<td>0</td>
</tr>
<tr>
<td>Valimäki et al</td>
<td>8</td>
<td>nIFN-alfa 3 MIU x 7/week SC</td>
<td>50</td>
<td>12.5</td>
</tr>
<tr>
<td>Öberg et al</td>
<td>37</td>
<td>nIFN-alfa 6 MIU x 7/week IM</td>
<td>49</td>
<td>11</td>
</tr>
<tr>
<td>Öberg et al</td>
<td>21</td>
<td>nIFN(^{2b}) 5 MIU x 3/week SC</td>
<td>53</td>
<td>0</td>
</tr>
<tr>
<td>Norheim et al</td>
<td>20</td>
<td>nIFN-alfa 6 MIU x 7/week SC vs streptozotocin + 5FU</td>
<td>50</td>
<td>0</td>
</tr>
<tr>
<td>Öberg and Eriksson</td>
<td>111</td>
<td>nIFN-alfa x 7/week SC</td>
<td>42</td>
<td>15</td>
</tr>
<tr>
<td>Janson et al</td>
<td>22</td>
<td>rIFN(^{2a}) 3 MIU/m(^2) x 3/week vs rIFN-alfa(^2a) 3 MIU/m(^2) x 3/week + streptozotocin + adriamycin</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>Biesma et al</td>
<td>11</td>
<td>rIFN-alfa(^{2b}) 2.5 MIU x 7/week SC</td>
<td>60</td>
<td>18</td>
</tr>
</tbody>
</table>
Malignant endocrine pancreatic tumors.

The studies listed in Table 2 demonstrate that, to a similar degree as was reported for long-acting somatostatin analogs, alfa-interferon inhibits both hormone release from the tumor cell (biochemical response) and tumor growth. More than 500 patients have been treated with this agent worldwide; the median dose was 5 million units 3-5 times per week, subcutaneously. However, only 11% of patients experienced tumor regression. When comparing data on tumor growth obtained with long-acting somatostatin analogs vs alfa-interferon, both therapeutic principles appear comparable. However, side effects of treatment with alfa-interferon are significantly more severe than those associated with long-acting somatostatin analogs.[29]

Combination of long-acting somatostatin analogs with alfa-interferon. Some case reports and 1 uncontrolled study suggest that the combination of both of the above therapeutic strategies is superior when compared against treatment with either compound alone.[29-31] These data have been prospectively evaluated by Dr. Arnold's group in Germany and their findings were reported for the first time at this symposium.

Dr. Arnold reported that in therapy-naive patients with neuroendocrine carcinoma, the combination of alfa-interferon plus octreotide was not superior in terms of progress-free (ie, disease progression free) survival or overall survival when compared with octreotide monotherapy. However, this does not exclude the possibility that the combination may be effective in patients not responding to monotherapy of either compounds as indicated by one uncontrolled trial.[31]

Chemotherapy. There are considerable data concerning the effects of chemotherapy on tumor growth and survival in patients with advanced metastatic neuroendocrine tumors that have recently been extensively reviewed.[32-34]

To summarize these data, endocrine tumors arising from the pancreas respond to a combination of streptozocin plus doxorubicin or streptozocin plus fluorouracil[35]; neuroendocrine malignancies arising from the mid- and hindgut (ie, carcinoids) or endocrine tumors originating from the stomach do not respond to these regimens. Dramatic improvement with these combinations has been repeatedly observed in patients with metastatic insulinoma and VIPoma (Werner-Morrison syndrome). Another indication for chemotherapy is the patient with anaplastic small-cell neuroendocrine carcinoma that responds to treatment with etoposide and cisplatin.[36] By contrast, patients with metastatic midgut tumors (patients with carcinoid syndrome) do not respond to any chemotherapy.

Somatostatin-Receptor Targeted Radiotherapy

Professor S. Pauwels, Head of the Department of Nuclear Medicine at Catholic University of Louvain in Brussels introduced a novel therapeutic principle consisting of a somatostatin peptide analog (Tyr3-octreotide) coupled to a complexing moiety (DOTA or DTPA) and labeled with a tightly bound beta-emitter (yttrium-90 or the diagnostic chemical analog, indium-111), especially a beta and gamma-emitter (lutetium-177). The utility of this peptide vector as an antineoplastic therapy for patients with somatostatin receptor-positive disease has been investigated in phase 1 and phase 2 trials.[37,38]

Based on very limited experience, this new treatment strategy appears promising for patients with neuroendocrine tumors and a high somatostatin receptor density. Partial remissions and
stabilization of tumor growth have been observed in more than 60% of patients. Side effects of treatment include bone marrow and kidney toxicity.

A final evaluation of this new treatment option is not possible at present; the results of additional adequately designed, controlled, and prospective studies are warranted.

Summary

The proceedings of this symposium, as presented at this year's United European Gastroenterology Week, clearly demonstrated that the diagnosis of patients with neuroendocrine tumors has been improved by the introduction of new pathohistologic techniques. These new techniques recognize the neuroendocrine origin of these tumors. Additionally, novel imaging applications using somatostatin scintigraphy have emerged as the most important novel techniques in this setting, with strong implications for treatment options.

The approach to treating patients with metastatic disease is still a matter of debate. Surgical tumor debulking is the first option in patients with limited disease. In patients with extensive disease, this author recommends starting with long-acting somatostatin analogs because of their limited side effects. In the case of tumor progression, this author recommends the addition of alfa-interferon to the regimen, but this strategy has not been proven prospectively.

If tumor growth cannot be inhibited by these measures, chemotherapy using streptozocin combinations can be offered to patients with neuroendocrine tumors of pancreatic origin, whereas patients with midgut tumors do not respond to this strategy. Etoposide plus cisplatin is reserved for patients with anaplastic small-cell neuroendocrine carcinomas. Somatostatin-receptor-targeted radiotherapy is a new and promising option that awaits further evaluation in prospective and controlled trials. In the case of metastatic disease to the liver, chemoembolization and liver transplantation may be considered.

References


