**Neuroendocrine Tumors and Their Humors**

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**Historical Overview**  
The origin of endocrinology is in the gastrointestinal tract. It began with Bayliss and Starling who instilled acid in the duodenum of dogs and showed the stimulation of the denervated pancreas secreted a bicarbonate rich fluid. They reasoned that this must be a hormone which means to excite thus gave birth to hormonology or endocrinology. Shown below is a graphic developed by Tom O’Dorisio which shows the multiple Nobel Prize events which followed the initial discovery. Most notable of these was the discovery of Insulin by Yalow and Berson which was the first “peptide therapy” to be followed by somatostatin as the second peptide introduced into therapy. Its importance in the localization of GI endocrine tumors, (Octreoscan) and subsequently use of its radiolabeled analog for ablation of tumors is illustrated. This evolution identified the secretion of peptides and amines into the lumen of the gastrointestinal tract referred to as “lumenology” and subsequently the labelling of somatostatin with Gallium a much more potent agent both for diagnostics (Gallium DOTATOC and DOTATATE and Peptide Receptor Radiotherapy (PRRT)).

**Significance of the Clinical Problem**  
NETs are a heterogeneous group of tumors that arise from the diffuse endocrine system. They derive from the embryological endocrine system predominantly in the gut in the gastric mucosa, the small and large intestine and the rectum but are also to be found in the pancreas, lung and ovaries. Neuroendocrine tumors (NETs) are tumors that arise from the diffuse endocrine system. They are slow-growing and capable of storing and secreting different peptides and neuroamines (2). Some of these substances cause specific clinical syndromes, others do not (3).

Some of these substances cause specific clinical syndromes whereas others do not. For convenience they are separated into functional in which the consequence is a clinical syndrome derived from the hormone or amine being produced or nonfunctional in which case the syndrome derives from the tumor bulk and the impact of metastases usually to liver, lymph
nodes and to bone. While considered rare, the annual incidence of NETs has risen to 40-50 cases per million due to the availability of improved techniques for tumor detection. A review of the SEER database showed a fivefold increase in the incidence of NETs from 1.09/100,000 in 1973 to 5.25/100,000 in 2004. In the United States, the prevalence is estimated to be 103,312 cases, which is twice the prevalence of gastric and pancreatic cancers combined (4).

Similar estimates have been reported from England and Sweden. These tumors occur at all ages with the highest incidence in fifth decade onwards except for appendiceal carcinoid which occurs at around 40y and the genetic syndrome such as Von Hipell Lindau, neurofibromatosis, tuberosclerosis, MEN1 and 11 have their onset many years earlier. Life expectancy is determined by the current grading system of tumors based upon the KI67 index of cell proliferation and the mitotic index.

**Barriers to Optimal Practice**
There are impediments to the diagnosis of NETs. They are not first in the differential as they comprise less than 2% of the gastrointestinal malignancies. Symptoms are often nonspecific and the manifestations mimic a variety of disorders. A delay in diagnosis can also happen when the biopsy material is not examined for the secretory peptides. Tumors may then be labeled erroneously as adenocarcinoma, affecting the management and underestimating prospects for survival (5). There is typically a delay of many years before the right diagnosis is made, by which time metastases have occurred and survival has directly been affected as shown in figure 1. Learning to recognize the symptoms is very important for early diagnosis. Clinically suspicious symptoms necessitate biochemical testing. Clinically suspicious symptoms necessitate biochemical testing.

**Learning Objectives**

**As a result of participating in this session learners should be able to:**

1. Recognize the clinical syndromes and different types of Neuroendocrine tumors responsible for the constellation of these features
2. Provide aids to differentiate NETS from masquerading diseases
3. Understand the choices of management and the use of an algorithm for clinical, biochemical and radiological diagnosis
4. Understand and make informed choices based upon a "decision tree" for management of NETS
### Major Clinical Manifestations

<table>
<thead>
<tr>
<th>Symptom/Sign</th>
<th>Percent</th>
<th>Tumor Production of Cytokines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flushing</td>
<td>84</td>
<td>TNF α, IL6, NFkB</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>79</td>
<td>Fever, Fatigue, Weight loss, Cachexia</td>
</tr>
<tr>
<td>Heart Disease</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>17</td>
<td></td>
</tr>
</tbody>
</table>

### Seldom Discussed Features

<table>
<thead>
<tr>
<th>Feature</th>
<th>Tumor Stimulation of antibody Formation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes, Metabolic Syndrome, NASH</td>
<td>(Ca++ channels(PQ), Achreceptors, CANCA,PANCA, Hu</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Neurological Syndromes</td>
</tr>
<tr>
<td>Neuromyopathy</td>
<td>Somatic and Autonomic Neuropathy</td>
</tr>
<tr>
<td>Pigmentation Arthropathy</td>
<td>Cerebellar Ataxia</td>
</tr>
<tr>
<td>Hyper/hypoglycemia, NIHGPS</td>
<td>Eaton Lambert Syndrome</td>
</tr>
<tr>
<td>Ulcer Disease, skin rashes</td>
<td>Myaesthenia</td>
</tr>
<tr>
<td>Psychological Disturbances</td>
<td>CIDP</td>
</tr>
</tbody>
</table>

### Strategies for Diagnosis, Therapy and/or management

The most important strategy is an alertness to the possibility of a NET. The most common variety is the carcinoid tumor. It is the result of hypersecretion of vasoactive amines (e.g., serotonin, histamine, tachykinins, and prostaglandins). It is common with small intestine NETs but also occurs with bronchial, ovarian and other foregut carcinoids (6). Because the liver can inactivate these substances, the carcinoid syndrome typically presents after hepatic metastasis have occurred. But this is not essential in foregut NETs.

The clinical manifestations are: flushing (which occurs in 84% of patients), Diarrhea (70%), heart disease (37%), but symptoms could also be widespread to include bronchospasm (17%) and myopathy (7%) (7) (8). Other recently recognized associated symptoms include: abnormal increase in skin pigmentation which is a pellagra like eruption (5%), arthropathy, paraneoplastic neuropathy, and edema (9). Mesenteric fibrosis is associated with midgut carcinoids even in the absence of a visible mass and could compress the vessels which leads to bowel ischemia and malabsorption.

The specific etiologic substances of each of the manifestations are not known. Serotonin, Prostaglandin, 5-HTP, Substance P, Kallikrein, Histamine, Dopamine, and Neuropeptide K are thought to be involved. Pancreatic polypeptide and motilin levels are often elevated. Several circulating tumor markers have been evaluated for the diagnosis and follow up of NETs; however a tissue confirmation is needed to make the diagnosis. The specific hormone causing the clinical syndrome should be measured e.g. gastrin, insulin, PP etc. and followed over time.
Potential diagnostic markers include: Chromogranin A, Chromogranin B and C, 5-HIAA, Pancreastatin, and Pancreatic polypeptide.

**Carcinoid heart disease**
It is characterized by fibrous endocardial thickening that mainly involves the right side of the heart. This fibrous tissue characteristically devoid of elastic fibers is known as carcinoid plaque. It causes retraction and fixation of the tricuspid and pulmonary valves which leads to valvular regurgitation, but pulmonary and tricuspid stenosis may also occur (10). The cause is unclear but direct actions of serotonin and bradykinin have been implicated in animal studies (11). The clinical presentation is that of right sided heart failure with fatigue, dyspnea, ascites, edema and cardiac cachexia. Left heart disease is uncommon.

**Bronchoconstriction**
It is clinically apparent as wheezing. The differential diagnosis includes asthma and COPD. The bronchospasm is usually caused by SP, Histamine, or serotonin (5).

**Blood and Urine Biomarkers Potentially Useful for Diagnosis and Follow Up**
Several circulating tumor markers have been evaluated for the diagnosis and follow up of NETs, however a tissue confirmation is needed to make the diagnosis. Measurement of specific hormones may be helpful and used in conjunction with imaging to follow clinical status and treatment response. There is controversy on the need for biomarkers and the frequency with which they should be sampled in following progress and or response to intervention. In some instances the relationship between the clinical syndrome and the hormone implicated is clear in which case the specific hormone causing the clinical syndrome should be measured and followed over time e.g. gastrin in gastrinoma syndrome. Other markers may also be secreted by less well differentiated tumors and nonfunctioning ones (3). The key is to identify few biomarkers in a particular patient and follow them over time in conjunction with symptoms and measurements of tumor bulk.

Potential diagnostic markers include Chromogranin A, Chromogranin B and C, 5-HIAA, Pancreastatin, and Pancreatic polypeptide

**Chromogranin A (CgA)**
CgA is a most important marker. It is a 49-KDa acidic polypeptide present in the secretory granules of all neuroendocrine cells. Its sensitivity varies between 53% and 68% and the specificity between 84 and 98% (12-16). A recent meta-analysis of 13 studies has shown a high sensitivity of 73% and specificity of 95% for the diagnosis of NETs (17). CgA level should be measured fasting and exercise should be avoided before the testing as both eating and exercise lead to increased levels (16). Somatostatin analogs affect the CgA level so the serial measurements should be done at the same interval from the injections.

There are caveats to the use of CgA as a universal tumor marker for NETs. First, the level of CgA correlates with tumor volume (18), hence small tumors may be associated with a normal level. Second, false positive measurements are reported in common conditions including: decreased renal function, liver or heart failure, chronic gastritis, inflammatory bowel disease, hyperthyroidism, PPI use, and even benign essential hypertension and exercise-induced physical stress (19,20). Also, elevations of CgA are reported in malignant non-neuroendocrine tumors like breast cancer and hepatocellular carcinoma (16). These problems are not seen with Chromogranin B (CgB) or pancreastatin (19).
Markers useful in follow up include: Pancreastatin which may help monitor response to surgery and predict tumor growth. Neurokinin A is a possible prognosticating marker when followed during treatment. Neuron specific enolase has a very low false negative rate which makes it a reasonable marker for follow up. MicroRNA profiling has entered the arena and when it becomes clearer what is being measured and what this reflects may remain a prophecy yet to be fulfilled. NETs can also be nonfunctional and present with signs and symptoms due to the mechanical complications (pain, obstruction, bleeding), but those silent tumors can at any point in time start producing hormones and become syndromic (7). The substance secreted by one tumor may change with time and yield an entire different clinical syndrome. Indeed, metastasis are known to each secrete different hormones than the parent tumor. NETs can also secrete other substances not related to their original cell properties like cytokines, autoantibodies, etc, which results in paraneoplastic syndromes (21). See Figure 1 for the frequent manifestations as well as the seldom discussed and unusual syndromes.

The substance secreted by one tumor may change with time and yield an entire different clinical syndrome. Indeed, metastasis are known to each secrete different hormones than the parent tumor. NETs can also secrete other substances not related to their original cell properties like cytokines, autoantibodies, etc, which results in paraneoplastic syndromes (21). See Figure 1 for the frequent manifestations as well as the seldom discussed and unusual syndromes. The clinical presentations, the syndromes that are produced, the tumor type the sites where the tumors are to be found and the hormones, amines and peptides synthesized and released into the periphery and which are responsible for many of the clinical features are given in the table below. In general NETs are named according to the hormone they produce (e.g. gastrinoma if gastrin secreting, VIPoma if VIP secreting). We do suggest an approach to diagnosing a NET based on the clinical presentation and the biochemical markers, as summarized in table 1.

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Syndrome</th>
<th>Tumor Type</th>
<th>Sites</th>
<th>Hormones</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flushing</td>
<td>Carcinoid Medullary Carcinoma of Thyroid Pheochromocytoma</td>
<td>Carcinoid C cell tumor Tumor of Chromaffin cells</td>
<td>Mid/ foregut Adrenal medulla Gastric Thyroid C cells Adrenal and Sympathetic Nervous system</td>
<td>Serotonin, GCRP, Calcitonin Metanephrine and Normetanephrine</td>
</tr>
<tr>
<td>Diarrhea abdominal pain and dyspepsia</td>
<td>Carcinoid, WDHHA, ZE, PP, MCT</td>
<td>Carcinoid, VIPoma, Gastrinoma, PPoma, Medullary carcinoma thyroid mastocytoma</td>
<td>As above, pancreas, mast cells, thyroid</td>
<td>As above, VIP, gastrin, PP, calcitonin</td>
</tr>
<tr>
<td>Diarrhea/steatorrhea</td>
<td>Somatostatinoma Bleeding GI tract</td>
<td>Somatostatinoma, neurofibromatosis</td>
<td>Pancreas Duodenum</td>
<td>Somatostatin</td>
</tr>
<tr>
<td>Wheezing</td>
<td>Carcinoid</td>
<td>Carcinoid</td>
<td>Gut/pancreas/lung</td>
<td>SP, CGRP, serotonin</td>
</tr>
<tr>
<td>Ulcer/dyspepsia</td>
<td>Zollinger Ellison,</td>
<td>Gastrinoma</td>
<td>Pancreas/duodenum</td>
<td>Gastrin</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Whipple’s triad</td>
<td>Insulinoma, sarcoma, hepatoma</td>
<td>Pancreas, retroperitoneal liver</td>
<td>Insulin, IGF1, IGF11.</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>Sweet Syndrome Pellagra</td>
<td>Glucagonoma Carcinoid</td>
<td>Pancreas Midgut</td>
<td>Glucagon Serotonin</td>
</tr>
<tr>
<td>Dementia</td>
<td>Sweet syndrome</td>
<td>Glucagonoma</td>
<td>Pancreas</td>
<td>Glucagon</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Glucagonoma Somatostatin</td>
<td>Glucagonoma Somatostatinoma</td>
<td>Pancreas</td>
<td>Glucagon Somatostatin</td>
</tr>
<tr>
<td>DVT, Steatorrhea, Cholelithiasis Neurofibromatosis</td>
<td>Somatostatin</td>
<td>Somatostatinoma</td>
<td>Pancreas Duodenum</td>
<td>Somatostatin</td>
</tr>
<tr>
<td>Silent, liver mets</td>
<td>Silent</td>
<td>PPOMA</td>
<td>Pancreas</td>
<td>PP</td>
</tr>
<tr>
<td>Fever</td>
<td>With weight loss and cachexia</td>
<td></td>
<td></td>
<td>Cytokines (IL-6, NF-kb, TNF-α)</td>
</tr>
</tbody>
</table>
Bone metastasis

<table>
<thead>
<tr>
<th>Bone metastasis</th>
<th>Pain/fracture/spinal compression</th>
<th>Any</th>
<th>Any</th>
<th>Bone Alk phos N-telopeptide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paraneoplastic syndromes</td>
<td>Peripheral neuropathy, myopathy, mystenia, CIDP, Lambert Eaton, cerebellar ataxia</td>
<td>Any</td>
<td>Any</td>
<td>Antibodies to calcium channels, acetylcholine receptors, C-ANCA, P-ANCA, Hu</td>
</tr>
</tbody>
</table>


**Flushing**

Although a cardinal manifestation of carcinoid syndrome it occurs in other conditions like: menopause, panic attacks, medullary thyroid cancer, autonomic neuropathy, mastocytosis, and simultaneous ingestion of Chlorpropamide and alcohol. Table 2 lists tests suggested to help with the differential and Table 3 suggests the various biomarkers.

**Features Associated with Different Flushing Syndromes**

<table>
<thead>
<tr>
<th>Flushing Syndrome</th>
<th>Associated Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoid</td>
<td>Diarrhea, Wheezing</td>
</tr>
<tr>
<td>Medullary Carcinoma Thyroid</td>
<td>Mass in Neck, family history</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>Paroxysmal hypertension, pallor tachycardia</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Autonomic Neuropathy, Chlorpropamide</td>
</tr>
<tr>
<td>Menopause</td>
<td>Cessation of Menses</td>
</tr>
<tr>
<td>Panic Syndrome</td>
<td>Phobias and anxiety</td>
</tr>
<tr>
<td>Mastocytosis</td>
<td>Dyspepsia, peptic ulcer, dermatographia</td>
</tr>
<tr>
<td>Polycythemia, renal cell carcinoma</td>
<td>Plethora</td>
</tr>
<tr>
<td>Food</td>
<td>Alcohol, MSG, Nitrites, Cheese, Tyramione containing foods, red wine, dark chocolate, hot dogs, dried fruit</td>
</tr>
<tr>
<td>Drugs</td>
<td>Niacin, phosphodiesterase inhibitors</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>Destitute</td>
</tr>
</tbody>
</table>

**CLINICAL CONDITION** | **BIOMARKERS**

| Carcinoid                  | Plasma 5HIAA, (22) 5HTP, SP, CGRP, CgA, pancreastatin, neurokinin A Pro BNP |
| Medullary carcinoma of the thyroid | Calcitonin, Calcium infusion RET proto-oncogene |
| Pheochromocytoma/paraganglioma | Plasma fractionated metanephrines and catecholamines, methoxytyramine, SHDBC |
| Autonomic neuropathy       | Heart rate variability, 2H post prandial glucose         |
| Menopause                  | Follicle stimulating hormone (FSH)                        |
| Epilepsy                   | Electroencephalogram (EEG)                               |
| Panic                      | Pentagastrin/ACTH                                         |
| Mastocytosis               | Plasma histamine, urine tryptase                           |
| Hypomastia, Mitral valve prolapse | Cardiac echo |

When the flushing is dry it is due to a carcinoid tumor until proven otherwise. The flush in foregut tumors tends to be of protracted duration, is often a purplish or violaceous hue and frequently results in telangiectasia and hypertrophy of the skin of the face and upper neck. The face may assume a “leonine” characteristic resembling that seen in leprosy or acromegaly. The flush in midgut tumors is of a faint pink to red color and involves the face and upper trunk down to the nipple line. It is initially provoked by alcohol and tyramine containing food like blue cheese, chocolate, red wine and red sausage. With time it becomes spontaneous. It usually lasts for few minutes and occurs many times a day. It generally does not lead to permanent discoloration of the skin.

Diarrhea

It is secretory in nature like all endocrine diarrheas. As opposed to osmotic diarrhea, it generates a large amount of stool with no osmotic gap and the key is that it persists with fasting. It occurs in other syndromes like: Watery diarrhea hypokalemia, hypochlorhydria, acidosis WDHHA syndrome (Verner-Morrison syndrome/VIPoma), Zollinger-Ellison syndrome (Gastrinoma), Calcitonin secreting tumors (medullary carcinoma of the thyroid or C cell hyperplasia), PPoma and Substance P secreting tumors.

In the gastrinoma syndrome the diarrhea is associated with steatorrhea and it improves with administration of a proton pump inhibitor (PP)I or histamine 2 (H2)-blockers. The acidity in the duodenum and small intestine inactivates lipase, amylase and trypsin, damages the mucosa of the small intestine and precipitates the succus entericus thereby causing malabsorption and steatorrhea.

In Verner-Morrison syndrome the diarrhea is associated with hypercalcemia. VIP stimulates gastrointestinal secretions and increases the rate of fluid delivery from the proximal to the distal small bowel so it exceeds its absorptive capacity. The diarrhea is watery and there is great loss of bicarbonate and potassium.

C-cell hyperplasia syndrome is a more recently described cause of secretory diarrhea and flushing. Total thyroidectomy is the treatment of choice.

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Table 2. Tests to identify causes of flushing (see Vinik and Chaya 2015) (1)

<table>
<thead>
<tr>
<th>5HIAA: 5 hydroxyindole acetic acid, 5HTP: 5 hydroxytryptophan, SP: Substance P, CGRP: Calcitonin gene related peptide, CgA: Chromogranin A</th>
</tr>
</thead>
</table>

Diarrhea

Character of Secretory and Osmotic Diarrhea

- Secretory persists with fasting
- Non-secretory improves with fasting

Gastroenterological
- **Secretory**
  - Large volume stools
  - Persists during fasting
  - 2X [Na⁺ + K⁺] = stool osmolality

- **Osmotic**
  - Small volume <1L/d
  - Disappears with fasting
  - 2X [Na⁺ = K+< stool osmolality i.e. osmotic gap, search for idiogenic osmoles

### Causes of Secretory Diarrhea

- Watery diarrhea, hypokalemia, hyperchlorhydria, acidosis syndrome
- Zollinger Ellison syndrome
- Carcinoid
- Medullary carcinoma of thyroid
- Secreting villous adenoma of rectum
- Surreptitious laxative abuse
- Idiopathic

### Imaging of NETs

The goal of imaging is to help make the diagnosis, determine the tumor burden and assess the potential for surgical resection, as well as establish the prognosis and determine the potential for non-conventional therapies especially in inoperable disease. Modalities include standard cross-sectional technique and nuclear functional imaging.

The sensitivity and specificity for some imaging modalities are shown in the table below: For a detailed discussion (see Vinik and Chaya 2015) (1).

#### Sensitivity, Specificity, Positive and Negative Predictive Values for Radiologic Diagnosis of NETS (7)

<table>
<thead>
<tr>
<th>TEST</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPP</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td>83%</td>
<td>76%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRI</td>
<td>93%</td>
<td>88%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>US</td>
<td>50-85%</td>
<td>76-97%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Octreoscan</td>
<td>52-78%</td>
<td>93%</td>
<td>98%</td>
<td>47%</td>
</tr>
<tr>
<td>PET/CT ⁶⁸Ga-DOTATOC</td>
<td>97%</td>
<td>92%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PET/CT ⁶⁸Ga-DOTANOC</td>
<td>78%</td>
<td>93%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PET/CT ¹⁸F-FDG-PET (NETs with proliferation index &gt;15%)</td>
<td>92%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Gene Studies as Biomarkers of NETs

The genetics of neuroendocrine tumorigenesis have yet to be elucidated.
Although small familial clusters of midgut carcinoids have been described, they are not associated with known genetic cancer syndromes. Among sporadic midgut carcinoids, several studies using comparative genomic hybridization or microsatellite markers have shown frequent allelic deletion of chromosome 18 (23) (24). On an epigenetic level, midgut NETs have been found to have global hypomethylation (25).

Genetic analysis should be performed in suspected cases of MEN1, VHL, neurofibromatosis-1, and tuberous sclerosis. Genetic counseling should be sought prior to testing in all patients. Germline DNA testing is recommended in the presence of a positive family history of MEN1, if there are suspicious clinical findings or if multiple tumors or precursor lesions are present. Somatic (tumor) DNA testing is not recommended (26) (27) (28).

Conclusions
Neuroendocrine tumors (NETs) are slow-growing neoplasms capable of storing and secreting different peptides and neuroamines. Some of these substances cause specific symptom complexes whereas others are silent. They usually have episodic expression and the diagnosis is often made at a late stage. Although considered rare, the incidence of NETs is increasing. For these reasons a high index of suspicion is needed. NETs on the increase, require high level of suspicion. We need to monitor the tumor burden, the clinical response and the appropriate biomarkers. There are biomarkers for specific NETs e.g. 5HIAA for carcinoid and hormones such as insulin, gastrin etc for secretory tumors. Markers for tumor behavior are Ki 67 sand mitotic indices of the tumor histology and circulating levels of Pancreastatin, neurokinin A, ChromograninA and neuron specific enolase. Surgical removal of the primary tumor is the first choice and one needs to be aggressive and use tumor debulking procedures of both the primary tumor and the metastases judiciously. Octreotide/Lanreotide controls symptoms and may cause biochemical and tumor burden improvement, Tumor growth can be arrested. One must treat to target plasma Octreotide/Lanreotide plasma levels around 10,000pg/ml which is half saturation of the somatostatin 2 and 5 receptors present on NETs. Management of liver metastases may require ancillary measures such as bland embolization, SIRS therapy radiofrequency ablation and chemoembolization. Therapy for somatostatin positive tumors can utilize somatostatin peptide receptor radiotherapy PRRT now becoming available in the USA. New therapies with agents acting on the RTK/PI3-K/AKT/mTOR pathway and new somatostatin analogs are in the pipeline.

In this article we review the different clinical syndromes and the pathophysiology of each tumor as well as the new and emerging biochemical markers and imaging techniques that should be used to facilitate an early diagnosis, follow up, and prognosis.

As Moertel once said 3 decades ago "this is an Odyssey in the land of slow growing tumors" We present here the evolution of this Odyssey and the rapid rate of progress that has been made in earlier and better identification with an increasing awareness and better tools for detection.

Case Presentations

Case 1
Mr. J N is a 51 year old male who is being seen today for follow up of his Carcinoid syndrome. He presented in 2007 with episodes of chest pain, dyspnea, feeling faint and flushing which was dry.

The episodes occurred frequently, over the face and of the rest of the body, lasted a few minutes and then disappeared without the development of telangiectasia. His 5HIAA was 50!

His physical examination was normal except for an ejection click at the left parasternal border with a soft systolic crescendo, decrescendo murmur at the left parasternal border. He has no myopathy, neuropathy, wheezing or prolonged FEV1 clinically and no proximal myopathy. He had an ileocolecotomy for a 1.5 cm tumor in the appendix which was positive for synaptophysin and CgA. The mitotic index as < 2% and the Ki67 index was 1%. He had features of Metabolic Syndrome, Mitral Valve Prolapse, Degenerative Disc Disease, Dyslipidemia and a History of Night Sweats. His main complaints today are - (1) No new issues. (2) Maybe a few less night sweats. (3) He cut back on the atenolol - stopped over the past month (tapered off over several weeks). He denies shortness of breath, palpitations or other issues. (4) He got his chest x-ray was normal and his PPD was negative. (5) He did not do any new labs. (6) His lower back is doing fine. He exercises several times a week - treadmill and abdominal and running. Because of the family history of Colon Ca and he has had the gene analysis.

He has had a return of the flushing post operatively but now it is wet, lasts a few minutes but his face is red and remains so after the flush. His carcinoid score is 2/13 with the only positive feature being the wet flushing. He has not developed shortness of breath or pedal edema and there is no liver enlargement, ascites or pedal edema. The lab results are: Normal CMP and ESR. Calcitonin<2 (0-8.4), Gastrin 18 (0-115), VIP <16.8 (0-58.8), Pancreatic Glucagon 80-(40-130), Pancreastatin 37(10-135) Neurokinin A 20 (<40), CgA 2(0-6.0) Substance P 106 (40-270). His plasma 5HIAA 10 ( ), FSH - 3.0; LH - 1.5 (1.7-8.6); ESR - 2; TT - 438; FT - 7.88; % FT - 1.80; SHBG -48.9)

Case 2

Mr JW was first seen here 11 years ago when he was 67. He complained of dyspepsia and reflux, was tired and fatigued and found to have a macrocytic anemia HB 8.0 and a routine colonoscopy and upper endoscopy was done and he was found to have a 1cm carcinoid tumor in the stomach with a mitotic index of <2% and a Ki 67 index of <2.0%. He had no diarrhea, wheezing or flushing. O/E BP 157/86, Pulse 54, Weight 154 lb he had no myopathy but he had some loss of vibration detection threshold in the feet, loss of ankle jerks and the laser Doppler blood flow indicated increase in blood flow in the feet as is seen in Charcot Neuroarthropathy.

Biochemistries: Serotonin 1119,CgA 69, CA19-9 2.5 CEA0.6, Histamine 0.27, Gastrin 1551,Calcitonin 7, Somatostatin 128, 5HIAA urine 375, insulin 3.4,Prolactin 6.5, PTH 39.2,Ca 9.9,Cortisol 26.8, gastric parietal antibodies 38.9 (0-20) ACTH 13

We offered him surgical therapy but he was reticent until 1 year later and he underwent an antrectomy which was extended to 66% gastrectomy when more carcinoid nodules were found in the stomach and a Billroth 11 was completed successfully.

Three years later he was feeling well without complaints except for mild dyspepsia and his primary care physician gave him Nexium which he said helped!! The biochemical workup revealed: CMP - Normal, except for fasting glucose - 113; BUN - 23; CO2 - 31; Globulin - 1.5; A/G Ratio - 3.0.

Substance P - 243; Chromogranin A - 8 (0-5) (was 4 on 12/12/11); Glucagon - 75; Histamine - 0.33; Neurokinin A - <5.0; Pancreatic Polypeptide - 186.5; Serotonin - 104; VIP - 81.4 (0.0-58.8) (was 70 on 1/3/12 and 76.5 on 12/12/11); Calcitonin - <2.0; Gastrin - 14; Pancreastatin - 77 (was 93 on 1/3/12).
1/9/12 - Urine 24-Hour 5-HIAA - 4.6.

* On 8/26/13 he presented with prolongation of FEV-1 and we ordered pulmonary function tests. Done: and was told "good for his age"

2014. He has had some dyspepsia and reflux, has become tired and lethargic, his skin is dry, hair is falling out and his voice is croaky. All NET makers normal, B12 1951, VIP 61.9 (0-58.8), histamine 0.46( 1.0) Gastrin <10. 5HIAA <10() , T4, F 1.4 T3T3 80, TSH 7.0, EKG low voltage and his resting heart rate is 54.

Case 3
AJ is a 70y old female presented in March 2008. with 4-5 months increasing spells of palpitations, headaches, flushing, tremors, weakness with paroxysmal episodes of hypertension (240/150 mmHg)hypertension for many years treated with – Coreg CR 80 mg/day; Benicar 40 mg/day; Tekturna 300 mg/day; Clonidine 0.1 mg four times daily; Verelan PM 200 mg/night; Lorazepam 1 mg every 4 hours for anxiety; Zocor 20 mg/day; Plavix 75 mg/day; Lasix 20 mg/day as needed; Potassium 20 mEq with Lasix; Fosamax 70 mg/week; Carafate 1 g four times daily; Albuterol nebulizer; Allegra 10 mg/day as needed.

She had Past Medical/Surgical Histories – Vitamin D deficiency; Iron deficiency since Billroth procedure (42 years earlier) for a bleeding ulcer; Hypertension; Carotid artery stenosis; Asthma; GERD; Osteoarthritis; Total abdominal hysterectomy (1993) secondary to fibroid tumors; Bladder lift (1987); Sinus operations (1994 and 1996).

Exam – BP – 178/79; Pulse – 78; Coughing spells with wheezing; Regular rate and rhythm with a systolic murmur and left carotid bruit.

Biochemistries – Plasma – Norepinephrine – 1,072 pg/mL (0-399 pg/mL); Epinephrine – 92 pg/mL; Dopamine – 33 pg/mL; Total Catecholamine – 1,197 pg/mL (0-642 pg/mL); Plasma – Metanephrines – 59 pg/mL; Normetanephrines – 125 pg/mL (18-111 pg/mL); Chromogranin A – 10 nmol/L (0-5 nmol/L); Urine 24-hour 5-HIAA – 10.5 mg/24-hrs (0-8 mg/24-hrs).

D/C clonidine; Start Dibenzyline (Phenoxybenzamine) – titrate slowly up from 10 mg once daily; Sandostatin LAR 30 mg once monthly; Left carotid artery stenting procedure performed in May 2008; Family History – Negative for carcinoid or neuroendocrine tumors; Positive for cancer (mother – cervical; brother – prostate).

June 2008 – Exploratory laparotomy; Lysis of adhesions; Extensive small bowel resection including mesenteric mass, and anastomosis > 20 tumors (size 0.3-2.0 cm); several invaded the serosa with positive satellite lesions in the mesentery; perineural and lymphovascular invasion with 5/6 lymph nodes positive for metastasis.

August/September 2008 - Follow up – Still flushing (like “eggs frying on my forehead and cheek”) - signifies hypertensive attack; “Zero energy;” (August 2008) BP – 135/69 mmHg/Pulse – 78; (September 2008) BP – 165/78/Pulse – 80; Still getting hypertensive episodes (240-250/120-130 mmHg) and going to the ED every few weeks

Blood Pressure Medications – Dibenzyline 240 mg four times daily; Demser 250 mg tid; Coreg 80 mg/day; Benicar 40 mg/day; Tekturna 300 mg/day; Verelan 200 mg/day. Biochemistries – Plasma Norepinephrine – 1,003 pg/mL; Epinephrine – 49 pg/mL; Dopamine – 16 pg/mL; Total Catecholamines – 1,068 pg/mL; Plasma Metanephrines – 87 pg/mL (12-60 pg/mL); Normetanephrines – 192 pg/mL (18-111 pg/mL). I-123 MIBG Scan (August 2008) – No definitive evidence for of MIBG avid tumor or significant interval change. OctreoScan (September 2008) – Decreased but residual somatostatin positive disease in the midline of the abdomen and pelvis.
No new area of disease identified. Abdominal exploration (November 2008) w/gamma probe – removal of mesenteric lymph nodes – 4/10 positive for carcinoid. Pathology – Synaptophysin/chromogranin positive; S-100 – negative, except for rare entrapped dendritic cells and adipocytes; Ki-67 - <1%. Fewer spells next few months but BP unchanged and fractionated metanephrines slight improvement.

Feb 2009 still having hypertensive episodes (200s/100s mmHg) – although no flushing to alert to episode – just “feel funny;” BP – 169/78 mmHg; Pulse – 58. 5HIAA normal! Octreoscan negative MIBG diffuse uptake in the lungs! CT innumerable pulmonary nodules bilateral. September 2009 Octreoscan negative and MIBG scan negative. Still hypertensive 162/66, pulse 61 added Norvasc 5mg/day and chlorothalidone 25 mg/day and Sunitinib 50 mg/day 2 weeks on and 2 weeks off.

December No flushing , 2 syncopal episodes, BP 120/60-150/100 reduced all medications became hypothyroid and need T4 replacement. Plasma Catecholamines - Norepinephrine - 3,757 pg/mL (0-400 pg/mL); Epinephrine - 104 pg/mL (0-100 pg/mL); Dopamine - 167 pg/mL (0-143 pg/mL); Total Catecholamines - 4,028 pg/mL (0-643 pg/mL); Plasma Metanephrines - 90 ug/mL (0-62 ug/mL); Plasma Normetanephrines - 535 pg/mL (0-145 pg/mL); Fasting glucose – 214 mg/dL (65-99 mg/dL). CT chest no metastases discontinued sandostatin and started Somatulin 120mg twice monthly.

July 2010 –BP, 130-140/80-90 with rare readings at 180/100).Biochemistries – Chromogranin A – 6 nmol/L; Pancreastatin – 63 pg/mL; Plasma Metanephrines – 45 pg/mL; Plasma Normetanephrines – 112 pg/mL. MRI Abdomen/Pelvis w/without contrast (June 2010) – No evidence of tumor recurrence or metastatic disease.
Case 4
Ms. L W is a 58 year-old female whose carcinoid was diagnosed in 3/19/2010. Her symptoms of edema, shortness of breath and fatigue with flushing occurred several times a day as did diarrhea which occurred when she was not eating. She was found to have bilobar hepatic metastases and periportal and periaortic lymph node involvement. The serotonin was >800 and the CgA 333. She initially received Octreotide 90 mg Q3/52 and in 5/12/2010 underwent an ileocollectomy. The cardiac ejection fraction was 55%. Between 2010 and 2013 she underwent SIRS, embolization of liver metastases or debulking with little impact on her symptoms of biochemistries. She had developed ascites, massive liver enlargement and peripheral edema with markedly elevated pulsatile JVP. The ejection fraction was 15% and she was shown to have mitral, tricuspid and pulmonary valve incompetence with fibrosis. She underwent mitral, tricuspid and pulmonary valve replacement and the cardiac status stabilized and she is pit of failure. However her biochemistries were grossly abnormal, she had profuse diarrhea, lost a great deal of weight and was admitted for failure to thrive. The diarrhea was only controlled with LAR 90 mg Q 3 weekly and somatostatin analog 500 ug am and 1000ug pm. She underwent a CT Chest, abdomen and pelvis. This showed no evidence of bone metastases. Intraabdominal carcinomatosis no change. Iliac lymph nodes increasing in size. No additional changes. A trial of Affinitor caused a pulmonary infection with nasal bleeding and thrombocytopenia. Xeloda was not tolerated and she received palliative 5 FU and leukovorin. Her ejection fraction returned to 55% and she left hospital having gained 20lb and was in great spirits. Her serotonin is 1500 and the pancreastatin >20,000 and the NKA is 80. WE reviewed her at tumor board and are considering further SIRS therapy. Alternatively we will do radioembolization.

Case Discussion and Answers

Questions

1. **Is the cause of the red face due to:**
   a. alcohol consumption
   b. hyperthyroidism
   c. diabetes facialis diabeticorum
   d. hindgut carcinoid
   e. midgut carcinoid
   f. mitral valve prolapse

Answer f mitral valve prolapse. He does not drink alcohol, he is clinically euthyroid and not diabetic, hindgut NETs to not case flushing and do not secrete serotonin or other vasodilators and midgut carcinoid flush is ephemeral lasting only minutes and do not leave a permanent discoloration. The relief of symptoms with atenolol is typical of mitral valve prolapse.

2. **Is this a type 1 carcinoid:**
   a. Is it a type 2 carcinoid
   b. Is it a type 3 carcinoid
   c. Is the hypergastrinemia due to the PPI
   d. was it correct to do an antrectomy
   e. Answer

This is a type 1 carcinoid of the stomach. There are three types of gastric carcinoid. Type 1 occurs with atrophic gastritis the most common cause being antibodies to gastric parietal cells which fail to secrete acid and the loss of suppression of gastrin unbridles its secretion. Gastrin is trophic to ECL cells and increase growth and proliferation leading to a gastric carcinoid. While
this can be controlled with somatostatin this is very expensive, requires shots for life and there are failures and a small but significant rate of malignancies. The hypergastrinemia is not due to the PPI which for the most part to dot case and increase of gastrin to > 400pg/ml and there is no need to do a secretin test. The presence of parietal antibodies combined with a neutral gastric pH would have been enough. Antrectomy is entirely appropriate. Type 2 occurs with MEN and there were no other hormone abnormalities and type 3 is sporadic and has the highest rates of malignancy and should require total gastrectomy.

Case 3

Question: What suggested to you that this patient had a paraganglioma combined with carcinoid?

a. Hypertensive crises
b. Elevation of both 5HIAA and fractionated metanephrines
c. Immunohistochemistry for synaptophysin, CgA in the mesenteric nodes
d. Responsiveness to Sunitinib
e. The need for more than 3 drugs to control BP including Demser.

Answer: None of the above. The secretion of norepinephrine and not epinephrine and the increased dopamine excluded a Pheochromocytoma and suggested paraganglioma. Hypertensive crises occur in both Pheochromocytoma and paraganglioma and the high levels of norepinephrine could derive from both Pheochromocytoma and paraganglioma and the fractionated metanephrines would not have made the diagnosis. Immunohistochemistry for CgA and synaptophysin simply recognizes an endocrine tumor. The hypertension in pheochromocytoma and paraganglioma is such to require large doses of antihypertensive agents. The response to Sunitinib of paragangliomas has now been established since this index case was reported!

Case 4

What are the findings that alert you to the possibility of carcinoid heart disease?

a. The symptoms of diarrhea and flushing
b. The cardiac ejection fraction of >50%
c. The elevated serotonin to 800 pg/ml
d. Pedal edema
e. Shortness of breath, elevated JVP and a mitral valve murmur of incompetence.

Answer

Pedal edema suggesting possible right heart failure. The symptoms of diarrhea and flushing occur in carcinoid syndrome. A cardiac ejection fraction is near normal. Carcinoid heart disease is almost always associated with serotonin values > 1000 pg/ml. Although it occurs left ventricular dysfunction is rare and not the rule in carcinoid diseases that shortness of breath with a mitral valve murmur is unexpected. The case illustrates how well we can do in the face of widely metastatic tumor, objectively addressing the cardia component and reducing tumor bulk to enhance responsiveness to standard therapy.


