THYMIC NEUROENDOCRINE NEOPLASMS

THE NEUROENDOCRINE SYSTEM: Historical Aspects

• 1928: Masson links “carcinoids” of the bowel to Kulchitzky cells by silver impregnation stains, and suggests that they are endocrine neoplasms
• 1938: Feyrter introduces the concept of a “diffuse neuroendocrine system”
• 1968: Pearse promotes the “APUD” theory of neuroendocrine neoplasia
• 1970’s: Concept of “neuroendocrine carcinomas” is introduced

CONCEPTS UNDERLYING THE UBIQUITY OF NEUROENDOCRINE TUMORS

1. A “neuroendocrine phase” of development is common to virtually every organ system during early morphogenesis, therefore linking neuroendocrine cells to “reserve” or “stem” cells in many fully-differentiated tissues and organs
2. The presence of differentiated normal neuroendocrine cells is NOT crucial to the development of neuroendocrine tumors in any given organ system
### NEUROENDOCRINE NEOPLASMS: Historical Terminology

<table>
<thead>
<tr>
<th>Tumor Location</th>
<th>Designation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pituitary</td>
<td>Pituitary adenoma/carcinoma</td>
</tr>
<tr>
<td>Thyroid</td>
<td>Medullary carcinoma</td>
</tr>
<tr>
<td>Lung</td>
<td>Bronchial carcinoid/bronchial adenoma</td>
</tr>
<tr>
<td>Several sites</td>
<td>“Atypical carcinoid”/APUDoma</td>
</tr>
<tr>
<td>Several sites</td>
<td>Oat cell (small-cell) carcinoma</td>
</tr>
<tr>
<td>Gut</td>
<td>Carcinoid/argentaffinoma/APUDoma</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Islet cell tumor/APUDoma</td>
</tr>
<tr>
<td>Adrenal</td>
<td>Pheochromocytoma</td>
</tr>
<tr>
<td>Adrenal/ANS</td>
<td>Neuroblastoma</td>
</tr>
<tr>
<td>Nose</td>
<td>Esthesio-(olfactory) neuroblastoma</td>
</tr>
<tr>
<td>Eye</td>
<td>Retinoblastoma</td>
</tr>
<tr>
<td>CNS</td>
<td>Medulloblastoma</td>
</tr>
<tr>
<td>CNS</td>
<td>Pseudoblastoma</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>Peripheral neuroepithelioma</td>
</tr>
<tr>
<td>Skin</td>
<td>Merkel cell (trabecular) carcinoma</td>
</tr>
</tbody>
</table>

### NEUROENDOCRINE NEOPLASMS: Updated (Simplified) Terminology

#### GROUP I TUMORS
- (Epithelial)
- Neuroendocrine CA
  - Grades 1, 2, & 3
- Classical Carcinoid
  - (Synonym for grade 1 NEC)

#### GROUP II TUMORS
- (Neural)
- Classic Neuroblastoma
- Olfactory Neuroblastoma
- Pheochromocytoma
- Paraganglioma
- PNET
  - — Medulloblastoma
  - — Retinoblastoma
  - — Pheochromocytoma
  - — Peripheral neuroepithelioma

### BIOLOGY OF NEUROENDOCRINE TUMORS: Major Concepts

1. All neuroendocrine neoplasms, regardless of type, are at least potentially-malignant lesions (i.e., there is no such thing as a “benign carcinoid tumor” or “benign islet cell tumor”)
2. Conventional morphological features of many neuroendocrine neoplasms cannot be reliably used to predict their behavior (e.g., classical carcinoid & pheochromocytoma)
3. Behavior of neuroendocrine tumors appears to be secondarily influenced by anatomic sites of origin and maximum tumor dimension
ULTRASTRUCTURAL FEATURES OF NEUROENDOCRINE DIFFERENTIATION

- Dense-core (neurosecretory)cytoplasmic granules, varying in size from 80 to 300 nm
- Granules are positive for the uranaffin method, but this is not usually required to distinguish them from other organelles (e.g., lysosomes)

IMMUNOHISTOLOGIC MARKERS OF NEUROENDOCRINE DIFFERENTIATION

- Chromogranin-A
- CD57 (Leu-7; HNK-1)
- Synaptophysin
- CD56 (Neural cell adhesion molecule)
- Specific amines & neuropeptides
- PGP9.5
MIXED/OCCULT NEUROENDOCRINE TUMORS

- Mixtures of clear-cut neuroendocrine tumors and just as obvious squamous carcinomas, transitional carcinomas, or adenocarcinomas, side-by-side (a probable example of “divergent” neoplastic differentiation)
- Poorly-differentiated/undifferentiated non-small cell carcinomas of various types & sites, with ultrastructural or immunohistological evidence of neuroendocrine differentiation; THESE ARE PARTICULARLY COMMON IN THE THYMUS

WHENCE THE “ATYPICAL CARCINOID?”

- “Atypical carcinoid” is no longer a useful clinicopathologic designation, because pathologists have, over the past 20 years, used this term as a wastebasket for pulmonary tumors with a variety of morphologic patterns (e.g., high-grade large-cell NEC, “intermediate cell” variant small-cell NEC, and organoid non-endocrine carcinomas of the lung)
- Treatment data on this entity are therefore hopelessly polluted
LARGE CELL NEUROENDOCRINE CARCINOMAS

• Formerly grouped with “atypical carcinoid” or with large cell carcinoma, not further specified; thymic neoplasms with such characteristics have been reported.
• Those nosological inaccuracies have adverse treatment-related impact, in that the behavior of large cell NECs is most like that of small cell NECs, and patients with the former neoplasms may benefit from chemotherapy that is directed at the latter tumors.

THYMIC NEUROENDOCRINE CARCINOMAS

• Rosai et al. described 8 cases of thymic tumors in 1972 (in Cancer) under the rubric of “mediastinal endocrine neoplasm, of probable thymic origin, related to carcinoid tumor;” this name was very quickly abbreviated to “thymic carcinoid”.
• In another publication in the same issue of Cancer, Rosai et al. documented the association between thymic carcinoids and MEN type I.

THYMIC NEC: Clinical Presentation

• Male to female ratio of 3:1; median age 43 yr.
  • Approximately 30% of patients are asymptomatic; another 20% have cough, chest pain, or SVC syndrome.
  • Approximately 50% have functional tumors, producing an endocrinopathy (Cushing’s syndrome, SIADH) or MEN type I.
  • Other associated conditions may include myopathy, neuropathy, Eaton-Lambert syndrome, and hypertrophic osteoarthropathy.
THYMIC NEC: Histological Variants

GRADE I:
- Organoid ("conventional")
- Diffuse (lymphoma-like)
  - Sclerotic
  - Oncocytic
  - Spindle-cell
- Pigmented (melanotic & lipofuscinoid)
  - Mucinous
  - Angiectatic
- Medullary carcinoma-like/amyloidotic

GRADE II:
GRADE III:

- Pure small-cell neuroendocrine carcinoma
- Pure large-cell neuroendocrine carcinoma
- Mixed small- and large-cell neuroendocrine CA
Grading of Neuroendocrine Carcinomas of the Thymus

• Outlined by Klemm & Moran (Semin Diagn Pathol 1999; 16: 32-41)
• Grade 1-- Organoid growth, nuclear uniformity, \( \leq 3 \) mitoses per 10 HPF, and only punctate, if any, necrosis
• Grade 2-- Areas of confluent sheet-like growth, noticeable nuclear pleomorphism, \( > 4 \) but \( < 10 \) mitoses per 10 HPF; obvious areas of necrosis
• Grade 3-- Images identical to SCNC or LCNC of the lung (in part or globally), with geographic necrosis & mitotic activity \( \geq 10 \) per HPF

Grading of Neuroendocrine Carcinomas of the Thymus: Comments

• In fact, there appears to be a two-tiered biological grading “scheme” for thymic NEC; grade I tumors have a relatively long evolution, and even patients with distant metastases may live for 10+ years; on the other hand, grades II and III tumors behave similarly (…aggressively)
• However, grade II and grade III tumors are more common than grade I in the thymus, by far
THYMIC NEC: Clinical Evolution

- Complete resection of tumor is possible in only roughly 50% of cases; however, thymic NEC may also be paradoxically encapsulated
- Aggressive surgical attempts at extirpation should be recommended; irradiation and chemotherapy are not particularly effective for thymic NEC
- Lymph nodal metastases in the chest are seen in ~70% of cases; 40-50% of patients develop extrathoracic metastases (to bone, liver, brain, lungs, & skin)
  - Overall mortality at 10 years’ followup is approximately 50%; death is due to intractable local recurrence or metastasis