Clinical Presentation

- **Pt:** 69-year-old Caucasian female
- **CC:** Progressive dry cough x 6 mos
- **PMH:** Increasing SOB and DOE for several years
  Rectal adenocarcinoma (2009)
- **PE:** Thyroid mass
- **Labs:** Normal (Chem panel, CBC, Coags, Urinalysis)
Patient Work-up

- Transbronchial core needle biopsy of lung
- 2 fragments of gray-tan tissue up to 1.1 cm
Eosinophilic islands = Congo Red + (not shown)
Biopsy Diagnosis

BIOPSY, RIGHT LUNG MASS:
• Compatible with metastatic Medullary Thyroid Carcinoma
Additional Work-Up

• FNA Biopsy 1:
  – “Paucicellular specimen with features suggestive of benign follicular nodule”

• FNA Biopsy 2:
  – “Consistent with colloid nodule”

• Repeat Ultrasound:
  – No additional lesions

Additional Work-Up, cont.

• Patient underwent surgery

• Right Middle Lobectomy
  – 74.2 grams
  – Overall size: 12 x 10 x 5 cm

• Dominant lesion
  – Pink-tan tumor nodule: 1.9 x 0.8 x 0.7 cm
  – Multiple, smaller surrounding nodules
Congo Red
Synaptophysin

Chromogranin

Calcitonin

CEA
Summary of Findings

Special stains
- Congo Red + (amyloid)

Immunostains
- Synapto: +
- Chromo: +
- Calcitonin: Weakly +
- CEA: -
- Ki-67: Low (< 1-2%)
But that’s not all....
Final Diagnosis?
Final Diagnosis

• Typical Carcinoid Tumor, arising in the setting of Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia (DIPNECH)

Tumors with Neuroendocrine Morphology

• Typical Carcinoid (Low-grade)

• Atypical Carcinoid (Intermediate grade)

• Large Cell Neuroendocrine Carcinoma (High-grade)

• Small Cell Carcinoma (High-grade)
Carcinoid Tumors

Typical Carcinoid Tumor
• Carcinoid morphology
• ≥ 0.5 cm
• No necrosis
• < 2 mitoses per 10 HPF
• Ki-67: <5%

Atypical Carcinoid Tumor
• 2-10 mitoses per 10 HPF
• Necrosis (often punctate)
• Ki-67: 5-20%

A Pre-invasive Lesion
WHO Classification

• Squamous dysplasia/in situ → Invasive SCC/Basaloid

• Atypical adenomatous hyperplasia (AAH) → Adenocarcinoma, lepidic type (Bronchioalveolar carcinoma)

• DIPNECH → Carcinoid Tumor(s)
Spectrum of Pulmonary NE cell Proliferations

Confined to BM

DIPNECH

Breach of BM

< 5 mm

Tumorlet

> 5 mm

Carcinoid

11q13 allelic imbalance
Pulmonary Neuroendocrine Cells (PNECs)

- Aka, “Kulchitsky cells”
- Specialized epithelial cells
- Found along entire respiratory tract
- Regulates fetal lung development
  - Present at 10 weeks
  - Paracrine secretion
  - Branching morphogenesis
- Adults: rare, single cells

PNEC Hyperplasia/Proliferation

- REACTIVE
- IDIOPATHIC / NEOPLASTIC

- Background lung:
  - Chronic lung damage
- Background lung:
  - Normal
  - Minimal focal fibrosis
Reactive PNEC Hyperplasia

• Observed commonly:
  – High altitude
  – Smokers
  – Various lung diseases:
    • Asthma, COPD
    • Cystic fibrosis
    • Others: Diffuse panbronchiolitis, eosinophilic granuloma

• Associated with:
  – Distortion of lung microstructure
  – Hypoxia

Idiopathic PNEC Hyperplasia: DIPNECH

• Definition: PNEC hyperplasia confined to respiratory epithelium without breaching of BM

• Various forms:
  – Linear proliferation
  – Small nodules
  – Diffuse

• Background lung:
  – Normal
  – Mild focal fibrosis
Which Came First?
Results in Obliterative Bronchiolitis-like picture

Hormone Secretion?

(DIPNECH)

FIBROSIS

HYPERPLASIA

Peptide Secretion

(Reactive)

Hyperplasia First:
DIPNECH & Bombesin

- 14 amino acid neuropeptide
- Secreted by PNECs
- Fibroblast growth factor

- Bombesin-pos. tumorlets
- Surrounding dense fibroelastic tissue
- Residual airway lumens virtually obliterated

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| HIS | GLY | VAL | ALA | TRP | GLN | MET | NH₂

GenScript Corp.
Clinical Presentation

- Demographics
  - Female
  - 5th or 6th decade
  - Non-smokers

- Symptoms
  - Cough, exertional dyspnea, chest tightness, wheezing, hemoptysis
  - May be present for years (>3yrs)

- Physical Exam
  - No consistent/definitive signs

- PFT
  - Obstructive or mixed pattern

SPIROMETRY FLOW-VOLUME LOOP

Normal Pattern

Obstructive Pattern
Diagnosis: Imaging

- **CXR/CT scan**
  - Mosaic pattern of air trapping
  - Multiple, bilateral small nodules
  - Patchy ground glass infiltrates
  - Bronchiectasis
  - Dominant lesion
  - If associated with carcinoid tumor -- usually peripheral in location

- **PET/CT**

Diagnosis

- **Initial testing:**
  - Bronchoscopy
    - Low yield with BAL & Bx
      - Larger tissue sample required to identify heterogeneous spectrum of lesions:
        » Diffuse hyperplasia
        » Tumorlets
        » Carcinoid

- **Gold standard:**
  - Surgical lung biopsy
**Prognosis**

- **DIPNECH only**
  - Slowly progressive condition
  - Benign course
  - Spans many years
  - Less commonly:
    - Severe respiratory obstructive symptoms

- **DIPNECH + Carcinoid**
  - Associated carcinoid tumors are indolent
  - Atypical features have not been described

**Treatment**

- **Surgical**
  - Resection of dominant lesion
  - If Carcinoid Tumor = Lymph Node Dissection
  - Lung transplantation (rare)

- **Medical**
  - Watch-and-wait approach
  - Steroids
  - Bronchodilators
  - Chemotherapy
  - Somatostatin analogs (SSA) or mTOR inhibitors
SSR and mTOR

- Neuroendocrine tumors:
  - Pulmonary
  - Extrapulmonary

- Consistent expression of:
  - Somatostatin receptors (SSRs)
    - Types 2 and 5 (inhibitors)
  - Mammalian Target of Rapamycin (mTOR) (protein kinase)

- Good clinical results with:
  - Somatostatin analogs (SSA)
  - mTOR inhibitors (e.g., rapamycin)

Summary

- Rare (possibly underrated)
- Women, 5th to 6th decades
- Generalized proliferation of PNECs
- Progresses to tumorlets & carcinoids
- Clinically mimics chronic lung disease
- Imaging mimics metastatic disease
- Benign course, excellent prognosis
References


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Questions?