**Neuroendocrine Tumors**  
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**PULMONARY NEUROENDOCRINE TUMORS**  
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**INTRODUCTION**
- Represent the clinico-pathological spectrum with variable morphological features and biological behavior.
- NE tumors - 25% of all malignant tumors of lungs (m.common SCLC)
- Arise from Kulchitsky cells present in the bronchial mucosa.

**Malignant tumors of lungs**
- Neuroendocrine tumors

**NEUROENDOCRINE SYSTEM (DES)**
- Neuroendocrine (Kulchitsky) cells are present in the bronchial mucosa and have the ability to synthesize, store, and secrete chemicals such as neuroamines and neuropeptides.
- Chemoreceptor role in the detection of hypoxia and may be involved in local epithelial cell growth and regeneration.
- Pulmonary neuroendocrine cells (PNECs) - solitary or may occur in clusters and form part of the dispersed or diffuse endocrine system.

**PICTURE of pathology**  
Slide of Kulchitsky cells here

**Spectrum of neuroendocrine cell proliferations in lungs:**
- NECH <5 mm, does not invade the basement membrane (arrow)
- Carcinoid tumorlet < 5mm, invades the basement membrane.
- Carcinoid tumor > 5 mm or more and invades the basement membrane.
- DPNECH

**DIFFUSE NEUROENDOCRINE SYSTEM (DES)**
- Neuroneuroendocrine cells (NEC) are widely distributed in the body regardless of their embryological origin.

**KULCHITSKY CELL**
- Neuroendocrine (Kulchitsky) cells are present in the bronchial mucosa and have the ability to synthesize, store, and secrete chemicals such as neuroamines and neuropeptides.
- Chemoreceptor role in the detection of hypoxia and may be involved in local epithelial cell growth and regeneration.
- Pulmonary neuroendocrine cells (PNECs) - solitary or may occur in clusters and form part of the dispersed or diffuse endocrine system.

**PICTURE of pathology**  
Slide of Kulchitsky cells here

**Clinical Findings:**
- Pre-neoplastic condition
- Older women ranging from 50 to 70
- Nonproductive cough and/or dyspnea / asthma
- Obstructive PFT

**Imaging findings:**
- Multifocal pulmonary micro-nodules
- With or without mosaic attenuation or air trapping from constrictive bronchiolitis
- Definitive diagnosis - biopsy
**NE LUNG TUMORS**

- **“Typical Carcinoid”**  
  - LOW GRADE

- **“Atypical carcinoid”**  
  - INTERMEDIATE GRADE

- Large cell neuroendocrine carcinoma (LCNEC)  
  - HIGH GRADE

- Small cell carcinoma

Non Small cell lung cancer with NE differentiation

Other with NE features: PNET, round cell tumor etc.

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**Carcinoid Tumor**

**Typical carcinoid (TC)**
- 80-90% of all pulmonary carcinoid tumors

- Non Smoker 40-60
- >F

- Clinical features
  - Central tumor - Hemoptysis
  - Peripheral tumor - Hyperinflation

- Least aggressive
  - Lymph node metastases ≤13%

- Paraneoplastic syndrome rare

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**Atypical carcinoid (AC)**
- ~10%-16% of all pulmonary carcinoid tumors

- Smoker 50-60
- >M

- Clinical features Same as TC

- More aggressive Malignancy
  - Lymph node metastases≥57%

- Paraneoplastic syndrome rare

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**IMAGING FEATURES CARCINOID TUMOR**

- Peripheral lesion:
  - Well defined nodule

- Central lesion:
  - Well defined, round or ovoid, lobulated mass hilar/periilar mass
  - Partial obstruction: air trapping or hyperinflation
  - Total occlusion: atelectasis, post-obstructive pneumonia, bronchectasis
  - Calcification ~30%
  - Homogenous enhancement

**TC & AC can’t be differentiated with imaging alone**

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**TYPICAL CARCINOID TUMOR**

19 M with hemoptysis and "non resolving pneumonia" and streaky hemoptysis

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**TYPICAL CARCINOID TUMOR**

43 F presented in the ER for SOB and elevated D dimer.

CT PE protocol : Bilateral pulmonary thromboembolic disease and an incidental mass in the right hilum (arrow).
In 111 Octreotide scan demonstrated intense uptake in the right hilar mass. No other uptake seen. Bronchoscopic Bx - Well differentiated neuroendocrine carcinoma

66 male presents with a new diagnosis of perihilar cholangiocarcinoma. Evaluate for metastatic disease

CT chest: Solitary Pulmonary nodule
FDG PET: no uptake
VATS resection: Atypical carcinoid

40-year-old woman presented with recurrent pneumonia in LLL. Endobronchial lesion seen in LLL bronchi on CT. Intense uptake on Ga 68 PET DOTATOC. Bronchoscopic Bx- well-differentiated low grade neuroendocrine carcinoma.

Mendes et al.

ADVANTAGE of PET Ga68 DOTATOC
1. Highly sensitive and specific
2. Whole body evaluation for metastasis.

- CT is excellent for detection of larger primary tumors and metastatic disease
- Carcinoid may show variable affinity for different radiotracers
- Combination of different imaging modalities - comprehensive map of disease as well as therapeutic implications

2007

77 F with persistent cough and recurrent pneumonia

NCCT: Partially calcified (arrow) right hilar mass
CECT: Intense heterogeneous enhancement
Patient lost to follow up...X 5 years
**LARGE CELL NEUROENDOCRINE CARCINOMA (LCNEC)**

In 1991, LCNEC identified as a higher grade neuroendocrine neoplasm, different from atypical carcinoid and SCLC. 3% of lung cancers in surgical series

**Clinical Findings:**
- M:F (95% are men)
- Mean age ~ 65 years
- Heavy smoking
- 25% asymptomatic
- Presenting symptoms
  - Chest pain
  - Hemoptysis
  - Cough
  - Dyspnea
  - Weight loss
- Paraneoplastic syndromes are rare
- Course: Right pneumonectomy - Malignant carcinoid

**Imaging Findings:**
- Large, peripheral pulmonary mass range 2-9 cm (most common)
- 20% centrally located with postobstructive effects
- Upper lobe - 63%
- Hilar and mediastinal lymphadenopathy
- Pleural effusion ~ 24%
- PET/CT increased uptake of FDG

**Clinical Findings:**
- Exclusively in smokers
- Equally in patients of both genders
- 2/3 metastatic at presentation
- Paraneoplastic syndromes SIADH, Cushing, Eaton-Lambert

**Presenting symptoms:**
- Cough
- Hemoptysis
- Chest pain
- Dyspnea
- Constitutional symptoms frequent
- Symptoms related to:
  - Local invasion (SVC syndrome in 10%)
  - Extrathoracic metastases (bone marrow suppression, bone pain, pruritus, jaundice, seizures, mental status changes, or ataxia

**Imaging Findings:**
- Large cell neuroendocrine carcinoma usually takes the form of a large, usually solitary, pulmonary mass, often centrally located with postobstructive effects. It may also present with hilar or mediastinal lymphadenopathy and pleural effusion.

**Pathology:**
- LCNEC is characterized by large cells with granular or vacuolated cytoplasm and large, vesicular nuclei with prominent nucleoli.

**Prognosis:**
- Prognosis is poor due to the aggressive nature of the tumor and the tendency for early metastasis.

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**SMALL CELL CARCINOMA (SMLC)**

Most common neuroendocrine lung neoplasm 20-25% of all invasive lung malignancies

**Clinical Findings**
- Exclusively in smokers
- Equally in patients of both genders
- 2/3 metastatic at presentation
- Paraneoplastic syndromes SIADH, Cushing, Eaton-Lambert

**Presenting symptoms:**
- Cough
- Hemoptysis
- Chest pain
- Dyspnea
- Constitutional symptoms frequent
- Symptoms related to:
  - Local invasion (SVC syndrome in 10%)
  - Extrathoracic metastases (bone marrow suppression, bone pain, pruritus, jaundice, seizures, mental status changes, or ataxia

**Imaging Findings:**
- Small cell carcinoma typically presents as a centrally located pulmonary mass with postobstructive effects. It may also present with hilar or mediastinal lymphadenopathy and pleural effusion.

**Pathology:**
- SMLC is characterized by small, round cells with scant cytoplasm and hyperchromatic nuclei.

**Prognosis:**
- Prognosis is poor due to the aggressive nature of the tumor and the tendency for early metastasis.

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**SMALL CELL CARCINOMA (SCLC)**

**Clinical Findings**
- Exclusively in smokers
- Equally in patients of both genders
- 2/3 metastatic at presentation
- Paraneoplastic syndromes SIADH, Cushing, Eaton-Lambert

**Presenting symptoms:**
- Cough
- Hemoptysis
- Chest pain
- Dyspnea
- Constitutional symptoms frequent
- Symptoms related to:
  - Local invasion (SVC syndrome in 10%)
  - Extrathoracic metastases (bone marrow suppression, bone pain, pruritus, jaundice, seizures, mental status changes, or ataxia

**Imaging Findings:**
- Small cell carcinoma typically presents as a centrally located pulmonary mass with postobstructive effects. It may also present with hilar or mediastinal lymphadenopathy and pleural effusion.

**Pathology:**
- SMLC is characterized by small, round cells with scant cytoplasm and hyperchromatic nuclei.

**Prognosis:**
- Prognosis is poor due to the aggressive nature of the tumor and the tendency for early metastasis.
**KEY POINTS**

- Pulmonary neuroendocrine cell proliferations and tumors arise from the Kulchitzky cells in the bronchial mucosa.
- NE tumors represent 20-25% of all invasive lung cancers, and the vast majority are small cell carcinomas.
- DIPNECH may be more common than was previously thought and may be misdiagnosed as metastasis. Considered a precursor of peripheral carcinoid tumor.

**MANAGEMENT AND PROGNOSIS**

**DIPNECH**
Patients are usually managed conservatively.
Prognosis - good, 83% of patients alive at 5 years.
Long-term follow-up is recommended to exclude nodule growth and development of carcinoid tumors and/or lymph node metastases.
Patients with symptoms of deteriorating respiratory function - treatment with corticosteroids, interferon-a, or chemotherapeutic agents.
Lung Transplantation - if refractory to medical treatment.

**LCNEC**
Surgical resection
Prognosis - poor
Median survival of 15-20 month.

**SCLC**
Limited stage - confined to the ipsilateral hemithorax, single radiation port, including mediastinal and supraclavicular lymph nodes - combined chemotherapy and radiation therapy, prophylactic cranial irradiation, and surgical resection of select limited stage tumors.
Extensive stage disease 60-70% - systemic chemotherapy with or without thoracic radiation.
Mean survivals of about 8-10 months.

**Typical carcinoid**:
- Lung resection
- Endobronchial resection with Nd-YAG (neodymium-doped yttrium aluminum garnet) laser or cryotherapy with or without adjuvant surgery.
- 5-year survival rates 87% - 94%
- 10-year survival rates 22-54%
- Recurrences - 10 years.

**Atypical carcinoid**:
- Aggressive resection and lymph node dissection with consideration of adjuvant chemotherapy.
- Preoperative lymph node sampling and staging.
- Metastatic / unresectable tumors - chemotherapy, immunotherapy, or radiolabeled agents such as somatostatin analog.
- 5-year survival rates 44% - 81%
- 10-year survival rates and 8% - 64%
- Recurrences - 10 years.

**SPECTRUM NEUROENDOCRINE TUMORS OF THE LUNG**

- Low grade < 2 mitosis
- Intermediate grade 2-10 mitosis
- High grade >10 mitosis

- Typical carcinoid
- Atypical carcinoid
- Large cell NE carcinoma (LCNEC)
- Small cell lung cancer (SCLC)

Worse prognosis.