Lung Cancer and Paraneoplastic Syndromes

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ACOI Board Review 2013
Introduction

- Lung cancer is the most common cause of mortality WORLDWIDE
- 1.3 million deaths per year

Incidence

Lung Cancer Incidence Rate by Sex, 1973-2008

Incidence: 2007

Lung Cancer Incidence Rates* by Race, Ethnicity, Gender, United States

*Rates are per 100,000 persons and are age-adjusted to the 2000 U.S. standard population (19 age groups - Census P25-1130).
†Hispanic origin is not mutually exclusive from race categories.

CDC and National Cancer Institute 2010
Cancer Survival Rates

The percentage of patients still alive five years after diagnosis, as seen below, has improved. But survival rates for lung cancer remain far lower for lung cancer patients than for patients with other cancers.

- Prostate: 1975-1977: 68.3%, 2002-2008: 99.2%
- Colorectal: 1975-1977: 50.1%, 2002-2008: 64.3%
- Breast: 1975-1977: 75.1%, 2002-2008: 89%
- Lung: 1975-1977: 12.3%, 2002-2008: 15.9%

Note: 2002-2008 figures reflect data from regions of U.S. with 28% of total population, while 1975-1977 data is drawn from regions with 9.5% of U.S. population. Survival rates include diagnoses at all stages.

Source: National Cancer Institute
5 year Survival Rates

Lung Cancer Diagnosis and Survival By Stage, 2001-2007

Risk Factors

- SMOKING
- Environmental
  - Radon
  - Air pollution
  - Metals
- Asbestos
- Genetics
- HIV
- Pulmonary Fibrosis
- Radiation therapy

Estimated Attributable Portion of Lung Cancer Cases by Cause

- Active Smoking: 90%
- Occupational Carcinogen Exposure: 9-15%
- Radon: 10%
- Outdoor Air Pollution: 1-2%

Lung Cancer

- Encompasses all tumors which arise from the bronchi, bronchioles, alveoli, and other respiratory epithelium
- Mesotheliomas, lymphomas, and sarcomas are distinct from the epithelial derived cancers
Lung Cancer

- Primary
  - Bronchogenic
  - Carcinoid
  - Adenoid Cystic Carcinoma
  - Mucoepidermoid

- Soft Tissue
  - Sarcoma

- Metastatic
Primary Lung Cancer: Bronchogenic Carcinoma

- Small Cell
  - Classic small Cell
  - Large Cell Neuroendocrine
  - Combined

- Non Small Cell
  - Squamous
  - Adenocarcinoma
    - Bronchoalveolar Cell
  - Large Cell
According to the WHO classification 88% of all primary lung neoplasms are made up of 4 different cell types:

- Small cell (Oat cell)
- Squamous (Epidermoid)
- Adenocarcinoma (Bronchioalveolar)
- Large cell (Large cell)
Incidence of Histologic Subtypes in the US Population

- Adenocarcinoma: 40%
- Squamous cell carcinoma: 30%
- Large cell carcinoma: 15%
- Small Cell: 15%
Small Cell Lung Cancer

- Classic features:
  - Usually Central
    - 2/3 perihilar/hilar
    - 1/6 in main bronchus, 1/6 peripheral or apical
  - Most aggressive of all tumors with rapid doubling time
  - Early metastases (nearly 70% metastatic at presentation)
    - Liver 30-35%
    - Bone 40-50%
    - CNS 15%
  - Strongest association: Tobacco Use
  - Early response to therapy (chemo and radiation) but eventually becomes refractory
Small Cell Lung Cancer

- **Limited Stage**
  - 30% of patients at presentation
  - Confined to one hemithorax

- **Survival**
  - Median survival is 15 to 20 months
  - 5-year 10-13%

- **Extensive Stage**
  - 70% of patients at presentation
  - Beyond one hemithorax

- **Survival**
  - Median survival is 8 to 13 months
  - 5-year 1-2%

*Median survival without treatment is 2-4 months*
Small Cell Lung Cancer

- Paraneoplastic syndromes
  - Ectopic ADH, ACTH
  - Lambert Eaton
- Treatment
  - Chemotherapy, XRT
  - Prophylactic cranial irradiation if attain complete response with initial treatment
- Survival not related to stage
Small Cell Lung Cancer
Small Cell Lung Cancer
**NSCLC: Squamous Cell**

- Best prognosis of the major cell types
- **Common Presentation:**
  - Large central mass
  - Obstructive symptoms/signs,
  - May cavitate 10%
  - Locally invasive, but can metastasize widely
- Intermediate growth rate - late metastasis
- Associated with smoking
- Hypertrophic pulmonary osteoarthropathy (HPOA) is NOT most common with squamous anymore
- Hypercalcemia
NSCLC: Squamous Cell
Squamous Cell Carcinoma
Squamous Cell Carcinoma
NSCLC: Adenocarcinoma

- **Common Presentation**
  - Peripheral in location
  - May metastasize widely before symptoms/signs develop
  - Not related to smoking

- **Most common type of bronchogenic carcinoma in NON-SMOKERS**

- **Slow growing but invades lymphatics and blood vessels**

- **May develop in or adjacent to fibrous lung “scar carcinoma”**
<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Immunoperoxidase staining</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoma</td>
<td>Epithelial stains (e.g., CK 7, 20 variable), EMA (+) CLA, S-100, vimentin (-)</td>
</tr>
<tr>
<td>Colorectal carcinoma</td>
<td>CK 7 (-); CK 20 (+)</td>
</tr>
<tr>
<td>Lung carcinoma</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>TTF-1 (+), Surf-A and Surf-B (+)</td>
</tr>
<tr>
<td>Other non-small-cell carcinoma</td>
<td>CK 7 (+), CK 20 (-), TTF-1 (-)</td>
</tr>
<tr>
<td>Small-cell carcinoma</td>
<td>TTF-1 (+), chromogranin (+), NSE (+)</td>
</tr>
<tr>
<td>Neuroendocrine carcinoma</td>
<td>NSE, chromogranin, synaptophysin (+), epithelial stains (+)</td>
</tr>
<tr>
<td>Germ cell tumor</td>
<td>HCG, AFP (+)</td>
</tr>
<tr>
<td></td>
<td>Oct4 transcription factor (+)</td>
</tr>
<tr>
<td></td>
<td>Placental alkaline phosphatase (+)</td>
</tr>
<tr>
<td></td>
<td>Epithelial stains (+)</td>
</tr>
<tr>
<td>Prostate carcinoma</td>
<td>PSA (+), rare false (-) and (+)</td>
</tr>
<tr>
<td></td>
<td>Epithelial stains (+)</td>
</tr>
<tr>
<td></td>
<td>CK 7 (-), CK 20 (-)</td>
</tr>
<tr>
<td>Pancreas carcinoma</td>
<td>Ca\textsuperscript{19-9} (+), CK 7 (+)</td>
</tr>
<tr>
<td></td>
<td>Mesothelin (+), trifoil factor 1 (+)</td>
</tr>
<tr>
<td>Breast carcinoma</td>
<td>ER, PR (+)</td>
</tr>
<tr>
<td></td>
<td>Her-2-neu (+)</td>
</tr>
<tr>
<td></td>
<td>CK 7 (+), CK 20 (-)</td>
</tr>
<tr>
<td></td>
<td>Gross cystic fluid protein 15 (+)</td>
</tr>
</tbody>
</table>
NSCLC: Adenocarcinoma
Adenocarcinoma
NSCLC: Adenocarcinoma
Mucin Stain
Presentation

- Usually peripheral
- Ground glass or infiltrative appearance
- Can be diffuse, unifocal, or multicentric
- +/- bronchorrhea

Tumor may NOT invade stroma, pleura, or vasculature

Lepidic growth

- Tumor cells line alveolar walls
Subtypes
- Nonmucinous
- Mucinous
- Mixed/Indeterminate (rare)

Increased risk with tobacco
- However – 30-40% are non-smokers
Bronchoalveolar Cell Carcinoma
Bronchoalveolar Cell Carcinoma
Bronchoalveolar Cell Carcinoma
NCSLC: Large Cell

- 95% are undifferentiated
- Present as large masses (similar to squamous cell)
- Centrally located
- Fairly uncommon - 3% of all lung cancers
- Rapid Growth / Early metastasis
- Giant Cell variant - even more lethal with mean survival less than 6 months
Large Cell Carcinoma
Lung Cancer: Other types

- Undifferentiated carcinoma
- Bronchial gland tumors
  - Adenoid cystic
  - Mucoepidermoid
- Other rare tumors
  - Sarcomatoid carcinoma
  - Carcinoid
    - Typical
    - Atypical
- Preinvasive lesions
Due to the enormous variance of history and therapeutic response, a correct histological diagnosis is necessary.

Over the past 25 years adenocarcinoma has become the histological subtype most frequently associated with both sexes and all races combined, replacing squamous cell.

The most common form of lung cancer arising in lifetime nonsmokers, in women, and the young (< 45 years) is Adenocarcinoma.
Small cell and epidermoid cancers present as central masses with endobronchial growth.

Adenocarcinomas and large cell cancers present as peripheral nodules/masses, with pleural involvement.

10% - 20% of Epidermoid and Large cell cancers cavitate. Squamous cell can cavitate.

Bronchioalveolar carcinoma is an adenocarcinoma arising from peripheral airways, presents as a single mass, diffuse multinodular lesion, or as a fluffy infiltrate.
Pancoast Syndrome

- Superior sulcus tumor
- Horner’s syndrome
  - Ptosis
  - Miosis
  - Anhydrosis
- Brachial plexus dysfunction
- Local erosion of vertebrae
Over 95% caused by malignancy
  › 5-10% lymphoma
Histology: predominantly small cell or squamous
May not be an “emergency” as previously thought
Approach:
  › establish histologic diagnosis
  › institute therapy promptly (usually XRT)
  › steroids, diuretics, phlebotomy may help
Superior Vena Cava Syndrome
Metastasis

- Every organ system is susceptible to lung cancer metastasis
- Brain metastasis with deficits neurologically
- Bone metastasis with pain and fractures
- Spinal cord compression from bone or epidural metastasis
- Invasion of the marrow with cytopenias
- Liver metastasis causing biliary obstruction
- Lymph node metastasis in supraclavicular region
- Adrenal metastasis are common but rarely cause insufficiency
Clinical Evaluation

- Stage Patient: clinical stage and pathologic stage
- History and Physical
  - Cough, hemoptysis, exposures
  - Weight loss
- CT of chest and abdomen/pelvis with contrast,
- PET (sensitive for metastasis, recurrence)
- CT Brain/MRI Brain
- Bone Scan
- Review of any prior films very important
- Tissue diagnosis
  - Bronchoscopy (degree of obstruction/recurrence)
  - Mediastinoscopy
  - VATS/Thoracotomy
Clinical Signs and Symptoms

- **Thoracic**
  - Cough
  - Hemothysis
  - Dyspnea
  - Pneumonitis
  - Pain
  - Wheezing

- **Paraneoplastic**
  - Nausea, vomiting, constipation (hypercalcemia)
  - Anorexia, wasting
  - Cushing’s syndrome
  - Hypertrophic pulmonary osteoarthropathy
  - Confusion, seizures (hyponatremia)
  - Thrombotic or embolic phenomenon (DIC)
  - Myasthenic syndrome (Eaton-Lambert)

- **Mediastinal**
  - Hoarseness
  - Venous engorgement (SVC)
  - Diaphragmatic paralysis

- **Metastatic**
  - Seizure, obtundation
  - Hemiparesis
  - Hepatomegaly, abdominal pain
  - Back pain
  - Bone pain, pathologic fracture
Most common symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Patients (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>45-74</td>
</tr>
<tr>
<td>Weight loss</td>
<td>46-68</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>37-58</td>
</tr>
<tr>
<td>Chest pain</td>
<td>27-49</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>27-29</td>
</tr>
<tr>
<td>Bone pain</td>
<td>20-21</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>8-18</td>
</tr>
</tbody>
</table>

Randomized controlled trials have not demonstrated a reduction in mortality from screening with chest X-ray or sputum cytology.

Newer technologies (spiral CT) may offer the ability to identify cancers at an earlier stage.

? Biochemical markers
## NSCLC: TNM Staging

### TNM staging system for lung cancer (7th edition)

#### Primary tumor (T)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>Tumor ≤3 cm diameter, surrounded by lung or visceral pleura, without invasion more proximal than lobar bronchus</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumor ≤2 cm in diameter</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumor &gt;2 cm but ≤3 cm in diameter</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor &gt;3 cm but ≤7 cm, or tumor with any of the following features:</td>
</tr>
<tr>
<td></td>
<td>- Involves main bronchus, ≥2 cm distal to carina</td>
</tr>
<tr>
<td></td>
<td>- Invades visceral pleura</td>
</tr>
<tr>
<td></td>
<td>- Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung</td>
</tr>
<tr>
<td>T2a</td>
<td>Tumor &gt;3 cm but ≤5 cm</td>
</tr>
<tr>
<td>T2b</td>
<td>Tumor &gt;5 cm but ≤7 cm</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor &gt;7 cm or any of the following:</td>
</tr>
<tr>
<td></td>
<td>- Directly invades any of the following: chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, main bronchus &lt;2 cm from carina (without involvement of carina)</td>
</tr>
<tr>
<td></td>
<td>- Atelectasis or obstructive pneumonitis of the entire lung</td>
</tr>
<tr>
<td></td>
<td>- Separate tumor nodules in the same lobe</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor of any size that invades the mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, or with separate tumor nodules in a different ipsilateral lobe</td>
</tr>
</tbody>
</table>

#### Regional lymph nodes (N)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>No regional lymph node metastases</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)</td>
</tr>
</tbody>
</table>

#### Distant metastasis (M)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
<tr>
<td>M1a</td>
<td>Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural or pericardial effusion</td>
</tr>
<tr>
<td>M1b</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>
Stage groups according to TNM descriptor and subgroups.

<table>
<thead>
<tr>
<th>T/M</th>
<th>Subgroup</th>
<th>N0</th>
<th>N1</th>
<th>N2</th>
<th>N3</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>T1a</td>
<td>Ia</td>
<td>IIa</td>
<td>IIIa</td>
<td>IIIb</td>
</tr>
<tr>
<td></td>
<td>T1b</td>
<td>Ia</td>
<td>IIa</td>
<td>IIIa</td>
<td>IIIb</td>
</tr>
<tr>
<td>T2</td>
<td>T2a</td>
<td>Ib</td>
<td>IIa</td>
<td>IIIa</td>
<td>IIIb</td>
</tr>
<tr>
<td></td>
<td>T2b</td>
<td>IIa</td>
<td>IIb</td>
<td>IIIa</td>
<td>IIIb</td>
</tr>
<tr>
<td>T3</td>
<td>T3 &gt;7</td>
<td>IIb</td>
<td>IIIa</td>
<td>IIIa</td>
<td>IIIb</td>
</tr>
<tr>
<td></td>
<td>T3 Inv</td>
<td>IIb</td>
<td>IIIa</td>
<td>IIIa</td>
<td>IIIb</td>
</tr>
<tr>
<td></td>
<td>T3 Satell</td>
<td>IIb</td>
<td>IIIa</td>
<td>IIIa</td>
<td>IIIb</td>
</tr>
<tr>
<td>T4</td>
<td>T4 Inv</td>
<td>IIIa</td>
<td>IIIa</td>
<td>IIIb</td>
<td>IIIb</td>
</tr>
<tr>
<td></td>
<td>T4 Ipsi Nod</td>
<td>IIIa</td>
<td>IIIa</td>
<td>IIIb</td>
<td>IIIb</td>
</tr>
<tr>
<td>M1</td>
<td>M1a Contra Nod</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
</tr>
<tr>
<td></td>
<td>M1a Pl Disem</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
</tr>
<tr>
<td></td>
<td>M1b</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
</tr>
</tbody>
</table>

NSCLC: Prognosis by Clinical and Pathological Stage

![Graphs showing survival rates for clinical and pathological stages of NSCLC](image)
NSCLC: Prognosis by Clinical and Pathologic Stage (median survival)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Clinical</th>
<th>Pathologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>60 months</td>
<td>119 months</td>
</tr>
<tr>
<td>IB</td>
<td>43</td>
<td>81</td>
</tr>
<tr>
<td>IIA</td>
<td>34</td>
<td>49</td>
</tr>
<tr>
<td>IIB</td>
<td>18</td>
<td>31</td>
</tr>
<tr>
<td>IIIA</td>
<td>14</td>
<td>22</td>
</tr>
<tr>
<td>IIIB</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>IV</td>
<td>6</td>
<td>17</td>
</tr>
</tbody>
</table>

Treatment of SCLC

- **LIMITED**
  - Radiation and Chemotherapy
  - PCI for complete responders
  - Occasionally surgery

- **EXTENSIVE**
  - Chemotherapy
  - PCI for complete responders
  - Radiation therapy for symptomatic metastasis (bone, epidural, brain)

Surgical treatment is rarely possible
Complete surgical resection
Postoperative adjuvant chemotherapy for Stage II and possibly Stage Ib
Patients who refuse chemotherapy or are not candidates may try radiation therapy
Locoregionally advanced disease due to primary tumor extension into extrapulmonary structures (T3 or T4) or mediastinal lymph node involvement (N2 or N3) without evidence of distant metastases (M0).

Chemo/Radiation
The following are major contraindications to curative surgery or radiotherapy alone in patients with non-small cell lung cancer:

- Extrathoracic metastasis
- SVC, vocal cord/phrenic nerve paralysis
- Malignant pleural effusion
- Cardiac tamponade
- Tumor within 2cm of carina
- Contralateral lung metastasis
- Bilateral endobronchial tumor
- Metastasis to supraclavicular lymph nodes
- Contralateral mediastinal node metastasis
- Main pulmonary artery involvement
Treatment

- Chemotherapy: clearly effective for small cell, but relatively poor results for non-small cell carcinomas
- Laser Therapy: Nd-YAG laser for palliation of obstructing endobronchial lesions
Beyond histologic features, the status of molecular targets, such as the epidermal growth factor receptor (EGFR) gene, has been shown to correlate with response to treatment with EGFR tyrosine kinase inhibitors in patients with relapsed or refractory disease and in the first-line therapy setting.

?Future
Treatment: SPN

- X-ray density that is surrounded by normal aerated lung, with circumscribed margins > 5cm
- 35% of such lesions are malignant (primary)
- “To resect or not to resect?” that is the question
- The following favors resection:
  - Young, large lesion, lack of calcification, chest symptoms, atelectasis, pneumonitis, adenopathy, growth revealed via x-rays
- Lack of growth over a > 2 year period and calcification would indicate a benign nature
- Dense central nidus, multiple punctate foci, “bull’s eye” (granuloma) and “popcorn ball” (hamartoma) calcifications suggest benign lesion
Mediastinal Mass

**Anterior mediastinum**
- Aneurysm
- Angiomatous tumor
- Goiter
- Lipoma
- Lymphoma
- Morgagni hernia
- Parathyroid tumor
- Pericardial cyst
- Teratoma
- Thymoma
- Thyroid tumor

**Middle mediastinum**
- Bronchogenic cyst
- Bronchogenic tumor
- Lymph node hyperplasia
- Lymphoma
- Pleuropericardial cyst
- Vascular masses

**Posterior mediastinum**
- Aneurysm
- Bronchogenic tumor
- Enteric cyst
- Esophageal diverticula
- Esophageal tumor
- Neurogenic tumor

- Trachea
- Esophagus
- Aorta
- Heart in pericardium
- Diaphragm
Benign Lung Neoplasms

- Represents < 5% of all primary tumors including:
  - Bronchial adenomas
  - Hamartomas (popcorn calcification)
  - Uncommon neoplasms
    - Chondromas, Fibromas, Lipomas, Hemangiomas, Leiomyomas, Teratomas, Pseudolymphomas
Benign Lung Neoplasms

- Can all present as central-masses causing
  - Airway obstruction
  - Cough
  - Hemoptysis
  - Pneumonitis

- The masses may or may not be visible on x-ray but are usually accessible to fiberoptic bronchoscopy

- Additionally these can present without symptoms as solitary pulmonary nodules
Bronchial Adenomas

- 80% are central
- Slow growing, endobronchial lesions
- Represent 50% of all benign pulmonary lesions
- 80-90% are carcinoids
- 10-15% are adenoid cystic tumors (cylindromas)
- 2-3% are mucoepidermoid tumors
Bronchial Adenomas

- Present in patients 15-60 years old as endobronchial lesions and are often symptomatic for several years.
- Bronchial carcinoids which usually follow a benign course express a neuroendocrine phenotype similar to the Kulchitsky cell.
- This cell is part of the Amine Precursor Uptake and Decarboxylase (APUD) System.
Carcinoids may secrete other hormones, such as ACTH, vasopressin, and cause paraneoplastic syndromes that resolve on resection.

Metastases may produce the carcinoid syndrome:
- Cutaneous flushing
- Cough, wheeze, dyspnea
- Diarrhea, N/V
- Pulmonic/tricuspid valve thickening
- Endocardial fibrosis
Bronchial Adenomas

- Are hypervascular and can bleed profusely after bronchoscopic biopsy
- Must be dealt with as potentially malignant and require resection for relief of symptoms and to prevent metastasis, which may produce paraneoplastic syndromes
- 5-year survival rate after resection is 95%
- 70% if regional lymph nodes involved
Hamartomas

- Peak incidence age 60 with a preponderance in males
- Histologically they contain normal pulmonary tissue components in a disorganized fashion
- Peripheral, clinically silent and benign in behavior
- Radiological findings are “popcorn” calcification
- The lesions usually have to be resected if patient is a smoker – VATS can be used to minimize problems
Paraneoplastic Syndromes

- Cushing Syndrome
- HPOA / Hypercalcemia
- SIADH
- Eaton-Lambert Syndrome
- Subacute cerebellar degeneration
- Dermatomyositis/Polymyositis
- Sensory Neuropathy
Paraneoplastic Syndrome associated with Lung Cancer

- Pathogenesis: Aberrant release of humoral mediators
  - Hormones/hormone-like peptides
  - Cytokines
  - Antibodies

- Occurrence: 10% of patients with lung cancer

- Expression: May precede diagnosis
Potential Mechanisms (Nathaison and Hall)

- Embryogenic excretion of stimulatory or inhibitory polypeptides
- Antigen:Antibody (Ag:Ab) – antigenic release of products of tumor cells
- Neurovascular reflexes
Neuroendocrine Tumors

- Spectrum of tumors
  - Small Cell
  - Well differentiated neuroendocrine tumor of the lung (atypical or malignant carcinoid)
  - Bronchial carcinoid
Systemic Features

- **Weight loss - anorexia, cachexia, fever (20%)**
- **Etiology:**
  - Tumor Necrosis Factor (TNF)?
  - Interleukin–1 (IL-1)?
  - Prostaglandins?
- **Rule out:**
  - Anemia
  - Infection
  - Malnutrition
  - Fluid and electrolyte disturbances
  - Drug reactions
Cutaneous Features

- Clubbing (hypertrophic pulmonary osteoarthropathy)

- Etiology:
  - Neurogenic (vagal)
  - Hormonal (↑ estrogen or growth hormone)
  - Vascular (A-V shunt and tissue hypoxia)

- Definition:
  - Soft tissue subungal thickening of fingernails

- Frequency:
  - 80% caused by bronchogenic cancer
  - Usually non-small cell
Digital Clubbing
Hypertrophic Pulmonary Osteoarthritis
Cushing’s Syndrome:

- Many lung carcinomas contain proopiomelanocortin (precursor to corticotropin) 50%
- Small cell carcinoma 1-5%
- Bronchial carcinoids 28-38%
- Symptoms: weakness, hyperglycemia, polyuria, hypokalemic alkalosis

Diagnosis:

- 24 hour urine-free cortisol excretion (overnight)
- 1 mg dexamethasone suppression test (can be confused with Pituitary Dependent Cushing’s)
Endocrine Features cont.

- Therapy:
  - Tumor removal or debulking
  - Ketaconazole
  - Aminoglutethimide
  - Metyapone
  - Odd therapy:
    - RU 486
    - Octreotide (somatostatin)
    - Selective adrenal embolization
    - Adrenalectomy
Hypercaldemia – Squamous cell

- Old idea – Metastasis to bone (small cell) but ↑ Ca2+
- Parathyroid hormone related peptide secreted
  - Increased bone reabsorption
  - Renal tubular reabsorption of Ca2+
  - Renal excretion of PO4
  - Renal excretion of cyclic adenosine monophosphate
Hypercalcemia – Squamous cell cont.

Therapy: rehydration by forced saline diuresis and calciuric agents (LASIX)

› Goal: ↓ bone reabsorption: ↑ Ca2+ excretion
  • Calcitonin (onset 4-6 hour, duration 24-48 hours)
  • Mithramycin – osteoclastic inhibitor
  • Bisphosphonates – not for squamous cell
  • Etidronate – not for Renal Failure (RF)
  • Pamidronate - not for RF
  • Gallium nitrate – 5 days 24 hour IV infusion
  • Parathyroid hormone receptor antagonists currently in research
 Syndrome of Inappropriate ADH (SIADH)

- Small cell 50% - only 1-2% have SIADH
- Increased RNA levels of Atrial Natriuretic Factor (ANF)
- Symptoms: confusion, seizures, coma – check Na+ (usually low)
- Therapy:
  - Limit fluids
  - Enhance free water excretion
  - Remove or debulk tumor
  - IV saline and loop diuretic
  - Demeclocycline (blocks ADH in kidney → Diabetes Insipidus)
  - Lithium carbonate?
Hematologic Features

- **Anemia** – 20%

- **Etiology:**
  - Chronic disease
  - Iron deficiency
  - Chemotherapy
  - Hemolysis
  - Bone marrow infiltration
  - Erythrocyte aplasia

- **Leukocytosis**
Hematologic Features
Coagulation abnormalities

- Thrombotic: Trousseau sign - Migratory Thrombophlebitis, PE, Thrombosis, Budd Chiari
  - Etiology:
    - Platelet activation?
    - Thrombosis
    - Procoagulant substances - secreted by tumor cells or macrocyte-macrophage
  - Therapy: Heparin, Thrombolytic agents

- Hemorrhagic - Dysfibrinoginemia
Neurologic Syndrome

- Small cell most common
  - Etiology: Autoimmune impairs Ca2+ channel activity which impairs release of acetylcholine
  - Eaton-Lambert Myasthenic Syndromes
    - Symptoms:
      - Proximal muscle weakness
      - Potential which enhances after 10-15 seconds of maximal voluntary contraction
    - Therapy:
      - 3,4-diaminopyridine (enhance release of actetylcholine)
      - Plasmaphoresis
      - Anticholinesterases
      - Immunosuppressive: steroids and azathioprine (IMURAN)
Other Neurologic features (Small cell)

- Subacute peripheral neuropathy:
  - Type 1 Anti Neuronal Nuclear Antibody (ANNA-1)

- Intestinal Dysmotilities:
  - Nausea, vomiting, abdominal discomfort, weight loss, altered bowel habits

- Limbic encephalitis:
  - Mental status changes and acute psychosis
  - ANNA-1?

- Necrotizing myelopathy:
  - ANNA-1?
  - Acute rapidly ascending paraplegia – rapid deterioration & death

- Visual:
  - Binocular loss - rare
  - ANNA-1?
“Lose some weight, quit smoking, move around more, and eat the carrot.”