Tumors

- Primary
  - Benign - Most common - Hamartoma
  - Malignant
    - Approximately 95% Carcinomas
    - Miscellaneous: Mesenchymal tumors, lymphomas
- Secondary (Metastasis)- lung is an extremely common site for metastasis

Hamartoma

- Benign neoplasm with various mesenchymal tissues
- Contains entrapped, “clefted” respiratory epithelium

Cartilage is the most common component
Clefts with respiratory epithelium
Lung Carcinoma
- Leading cause of cancer deaths
- 222,500 new cases in 2017 (M>F, 13.2% of all new cancer cases)
- 155,870 DEATHS estimated in 2017 (M>F, 25.9% of all cancer deaths)
- Percent surviving 5 years 18.1%
- Peak incidence 40-70 years

American Cancer Society

ETIOLOGY

Some Interesting Facts – Tobacco Smoking
- More than 1200 substances have been defined in cigarette smoke
- Approximately 90% of lung carcinomas occur in active smokers or those who stopped recently
- Average smokers - 10x greater risk of developing lung cancer
- Heavy smokers (more than 40 cigarettes per day for several years) have a 60x greater risk.
- Women more susceptible than men.
- Passive smoking increases risk 2X as compared to non-smokers
- Cessation of smoking decreases risk but may not return to baseline
- Associated with p53 alterations
Other influences may act in concert!

- **Industrial Hazards**
  - High-dose ionizing radiation
  - Asbestos
    - 5x by itself
    - 55x in smokers
- **Air Pollution**
  - Radon
- **Genetic predisposition**

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**Key Molecular Players**

- **Molecular Genetics**
  - **Dominant oncogenes:** C-MYC, KRAS, EGFR, c-Met, C-KIT
  - **Tumor suppressor genes:** p53, RB1, p16 (INK4a), other genes on chromosome 3 (FHIT, RASSF1A, etc)

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![Concept of Two-Compartment Model of Molecular Pathogenesis in Lung Cancer](image-url)

SCLC - small cell lung carcinoma, SQC - squamous cell carcinoma, ADC - adenocarcinoma
Clinical features of lung cancer

Most common complaints:

- Cough
- Weight Loss
- Chest pain
- Dyspnea

Clinical features of lung cancer

- Pneumonia, abscess - tumor obstruction of airway
- Pleural effusion - tumor spread into the pleura
- Pericardial tamponade - pericardial involvement
- Hoarseness - recurrent laryngeal nerve invasion
- Dysphagia - esophageal invasion
- Diaphragm paralysis - phrenic nerve involvement
- Rib destruction - chest wall invasion

Clinical features of lung cancer

- Superior vena cava syndrome i.e. facial swelling, cyanosis, dilatation of veins in head and neck - SVC involvement
Clinical features of lung cancer

- Pancoast tumors
  - Apically located/Superior sulcus tumors
  - Can destroy 1st/2nd rib
  - May show Horner syndrome
- Horner syndrome - due to cervical sympathetic plexus involvement (apical tumors)
  - Ptosis,
  - Anhidrosis
  - Miosis,
  - Enophthalmos
  - Loss of ciliospinal reflex

Clinical features of lung cancer

- Paraneoplastic Syndromes
  - Symptoms that occur in patients with cancer that cannot be readily explained by local or distant spread or by the elaboration of hormones not indigenous to the tissue or origin of the tumor

Paraneoplastic Syndromes

- SIADH: 5-10% pts, 60-70% of patients have subclinical abnormalities in renal excretion of free water, resulting in hyponatremia.

- Cushings: 3-7% of patients with small cell carcinoma, 30-40% increased serum ACTH. In addition to ACTH, these tumors often produce fragments of ACTH.

- Calcitonin: 50-60% of patients have been noted to have elevated calcitonin levels.
Clinical features of lung cancer

Other systemic manifestations

- Eaton-Lambert:
  - Muscle weakness
  - Most commonly associated with small cell carcinoma.
  - Autoantibodies against calcium channel.

- Sensory neuropathy
- Dermatologic abnormality (e.g. acanthosis nigricans)
- Hyperthrophic pulmonary osteoarthropathy (clubbing)

Simplistic Classification – Lung Carcinoma

Lung carcinoma

Small cell carcinoma
Approx 20%

Squamous cell carcinoma
25-30%

Non-small cell carcinoma
Approx 80%

Adenocarcinoma
30-40%

Unclassifiable/Large cell
tumor
10-15%

Tumors of the Lung -Terminology

Histologic Classification of Malignant Epithelial Lung Tumors

- Small cell carcinoma
- Squamous cell carcinoma
- Adenocarcinoma
  - Acinar, papillary, bronchioloalveolar, solid, mixed subtypes
- Large cell carcinoma
  - Large cell neuroendocrine carcinoma
  - Adenosquamous carcinoma
  - Carcinomas with pleomorphic, sarcomatoid, or sarcomatous elements
- Carcinoid tumor
  - Typical, atypical
  - Carcinomas of salivary gland type
- Unclassified carcinoma
Squamous cell carcinoma

- Background
- Precursor
- Morphology
- Molecular alterations

• More common in men
• Associated with smoking history
• Maybe associated with inappropriate PTH secretion- elevated Ca
• Arise centrally
• Associated with squamous metaplasia, dysplasia, carcinoma-in-situ (progression takes several years
• Will show intercellular bridges or keratinization or diffuse p63/p40 immunoreactivity with high molecularweight keratins (CK5/6)
• Local nodes involved in 70-90%
• Spreads outside the thorax, later than other histologic types
• 5-7.5% : 5 year survival

http://library.med.utah.edu/
Precursor Lesions for SQC

Increasing nuclear pleomorphism, loss of nuclear polarity, mitotic figures

Intercellular bridges

Keratinization

Bright Orange: Keratinized cells

Cytology: PAP stain

http://pathology.jhu.edu/
Squamous cell carcinoma
Molecular Genetics

- **Highest frequency of p53 mutations**
- Others include CDKN2A, PTEN, PIK3CA, NOTCH1, RB1
- Very rare EGFR and KRAS mutations

Adenocarcinoma

- Background
- Precursor
- Morphology
- Molecular alterations
- Treatment

Adenocarcinoma
- Relatively more frequent in women (most common type in women)
- More peripheral, but can be central also
- Less strongly associated with smoking (most common type in non-smokers)
- Progresses through AAH – AIS
- Spiculated mass, central scarring
- Adenocarcinoma: gland forming or mucin containing or TTF-1 positive
- Slower growing, smaller mass but can metastasize early
- Local nodes involved in over 50%
- 10-12% 5 year survival
Irregular spiculated mass with entrapped anthracosis

Spiculated lung mass on CT

http://library.med.utah.edu/

Precursor lesions

- Atypical Adenomatous Hyperplasia (AAH)
- Adenocarcinoma in situ (AIS)
- Minimally invasive adenocarcinoma
**Precursor lesions - contd**

<table>
<thead>
<tr>
<th>AAH</th>
<th>AIS</th>
<th>MIA</th>
</tr>
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<tbody>
<tr>
<td>Well demarcated</td>
<td><strong>AIS</strong></td>
<td><strong>MIA</strong></td>
</tr>
<tr>
<td>focus</td>
<td>- Formerly known as Bronchioloalveolar carcinoma (BAC)</td>
<td>✓ 3 cm or less</td>
</tr>
<tr>
<td>- Less than 5</td>
<td>- 3 cm or less</td>
<td><strong>AND</strong></td>
</tr>
<tr>
<td>mm</td>
<td>- Grow along pre-existing structures</td>
<td>✓ Invasive focus less than 5 mm</td>
</tr>
<tr>
<td>- Lined by cuboidal</td>
<td>- Preservation of alveolar architecture</td>
<td>✓ No invasion into pleura, lymphatics or blood vessels</td>
</tr>
<tr>
<td>to low columnar</td>
<td>- NO INVASION</td>
<td></td>
</tr>
<tr>
<td>epithelium</td>
<td></td>
<td></td>
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<tr>
<td>- Mild atypia</td>
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</tbody>
</table>

**Alveoli lined by cuboidal epithelium with mild atypia**

**Normal alveoli**

Cellular proliferation along septae without invasion

Moderate to marked atypia
Thyroid Transcription Factor 1

Invasive adenocarcinoma

Subtypes of Adenocarcinoma

a. Acinar adenocarcinoma
b. Papillary adenocarcinoma
c. Solid adenocarcinoma
d. Mucinous adenocarcinoma
Several driver mutations in ADC

- **EGFR mutations**
  - 30-40% Asians and 10-15% Caucasians
  - Females
  - Never-smokers
  - Mutations occur in the kinase receptor of the tyrosine kinase domain resulting in constitutive activation
  - Targeted therapy available with EGFR inhibitors: eg Erlotinib

- **ALK gene fusions**
  - ALK fusions also seen in large cell lymphoma (not the exact same fusion)
  - Younger patients
  - Never smokers
  - Targeted therapy with ALK inhibitors- eg. Crizotinib

- **KRAS mutations**
  - Most common mutation in Caucasian population (30%) and 10% in Asian population
  - Mutations correlate with worse outcome
  - Confer resistance to EGFR inhibitors
  - No specific targeted therapy
Large cell undifferentiated carcinoma

- Undifferentiated
- Diagnosis of exclusion
- Poor prognosis
- Metastasize to
  - liver, adrenal, brain
- 2-3% 5 year survival

Large cell carcinoma: No squamous or adenocarcinoma differentiation by morphology or by immunohistochemistry

Small cell carcinoma = Oat cell carcinoma

- Rapidly growing, high grade neuroendocrine tumor
- Central
- Strong association with smoking
- Widely metastatic
- Paraneoplastic Syndromes
  - ACTH, ADH
- Rarely resectable
- Tx: Radiotherapy and chemotherapy
- 5-8% 2 year survival
**Histologic characteristics**

- Densely packed “small blue” tumor
- “small”: size is about 3 times that of small, resting lymphocyte
- Round to ovoid nucleus
- Scant cytoplasm
- Finely dispersed chromatin
- Inconspicuous nucleoli
- High mitotic activity
- Necrosis present

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**Small cell carcinoma**

**Molecular Genetics**

- Inactivation of p53 in 100% of cases
- Inactivation of RB in 100% of cases
- Losses of 3p, 4q, 5q, 13q and 15q
Bronchial Carcinoid

- Low grade malignant neuroendocrine tumors
- Locally invasive, rarely metastatic
- Earlier age (40 years)
- Often resectable and curable
- Clinically: Carcinoid syndrome (rare) - intermittent diarrhea, flushing, and cyanosis
- Further classified into
  - Typical (low mitotic rate and absent necrosis)
  - Atypical (more frequent mitosis and focal necrosis)
- 50-95% 5 to 10 year survival
- TYPICAL CARCINOID – ATYPICAL CARCINOID - SMALL CELL CARCINOMA: SPECTRUM OF NEUROENDOCRINE TUMORS WITH INCREASING MALIGNANT POTENTIAL

A. Polypoidal endobronchial mass, no necrosis

B. Nests of bland cells, separated by vascular network

Why is the distinction among histologic types important?

- Small cell carcinoma – generally has widespread mets at the time of diagnosis, needs chemotherapy with or without RT
- NSCLC - generally resectable disease if early stage
- Certain chemotherapy agents contraindicated in squamous cell carcinoma - eg: Bevacizumab, Pemetrexed
- Targeted therapy available for adenocarcinoma
Mesothelioma

- Origin: Pleura (mesothelial cells)
- Spreads widely in pleural space **invasive by contiguous spread or diffuse seeding of pleural space**
- Uncommon tumor
- Related to asbestos
- 2-10% of heavily exposed pts develop mesothelioma in 20-50 year
- Survival > 1 year is rare

Mesothelioma

- Cytogenetics: Deletions in chromosomes 1p, 3p, 6q, 9p, or 22q
- Somatic mutations of tumor suppressor genes
  - p16/CDKN2A : on 9p21
  - NF2 : on 22q12
Mesothelioma - Histologic types

- Epithelioid (most common)
- Sarcomatoid
- Mixed

H&E stain: Mesothelioma, epithelioid variant

Immunohistochemical stain: Calretinin, strong nuclear and cytoplasmic positivity

Ferruginous Body

Asbestos Body
Mesothelioma - Electron Microscopy

Clinical Presentation
- Chest pain
- Dyspnea
- Recurrent pleural effusion

Outcome
- Poor prognosis (1 year survival 50%)
Metastasis

- Any cancer can metastasize to the lungs
- Common recipient
- The following neoplasms are most likely to spread to the lungs:
  - Melanoma
  - Thyroid cancer
  - Breast cancer
  - Colorectal cancer
  - Head and neck cancer
  - Renal cell cancer
  - Choriocarcinoma
  - Testicular cancer
  - Osteosarcoma
  - Ewing sarcoma
  - Wilms tumor
  - Rhabdomyosarcoma
  - Prostate cancer

Metastatic signet ring adenocarcinoma

Summary

- Epidemiology
- Clinical features
- Precursor lesions
- Histologic types
- Clinical significance of histologic typing
Case vignette

80-year-old woman presents with progressive dyspnea on exertion for the past 2 months. She also has a cough with daily clear sputum. No hemoptysis and no associated chest discomfort or pain. She has felt some "fluttering" sharp pain in the right lower chest that comes and goes.

She has a history of CAD, MI, and a remote history of a "breast neoplasm". She smoked from age 20 - 65 -- most of those years about 1/2 ppd (about 25 py). Father was a construction worker and died of emphysema, brother died of lung cancer. She admits to 10lb weight loss within the past 6 months.

CT: Showed a large mass. CT guided biopsy was performed.
Which biochemical abnormality is likely to be seen in this patient?

- Hypoglycemia
- Hyponatremia
- Hypermotremia
- Hypokalemia
- Hyperkalemia
- Hypercalcemia

Thank You!

Please do not forget to put in your E-vals