Lung Tumors

Overview:
- Frequent site of metastases from cancers arising in extrathoracic organs
- Primary lung cancer is also a common disease and accounts for leading cause of cancer related deaths (see ppt for statistics)
- 95% of primary lung tumors are carcinomas; the remaining 5% constitute a miscellaneous group that includes mesenchymal malignancies (e.g., fibrosarcomas, leiomyomas), lymphomas, and a few benign lesions.
- The most common benign tumor is a spherical, small (3 to 4 cm), discrete “hamartoma” that often shows up as a so-called coin lesion on chest radiographs. It consists mainly of mature cartilage, but this is often admixed with fat, fibrous tissue, and blood vessels in various proportions. Clonal cytogenic abnormalities have been demonstrated, indicating that it is a benign neoplasm, although still commonly referred to as hamartoma.
- Hamartoma is defined as a mass of disorganized tissue indigenous to the particular site. For example a hamartoma in the lung can be composed of disorganized mass of cartilage, submucous glands, respiratory epithelium etc.

ETIOLOGY AND PATHOGENESIS
- Smoking-related carcinomas of the lung arise by a stepwise accumulation of a sequence of many non-random genetic abnormalities that result in transformation of benign progenitor cells in the lung into neoplastic cells. Example: inactivation of the tumor suppressor gene located on the short arm of chromosome 3 (3p) is an early event, whereas TP53 mutations or activation of the KRAS oncogene occurs relatively late.
- About 90% of lung cancers occur in active smokers or those who stopped recently. There is a near linear correlation between frequency of lung cancer and pack-years of cigarette smoking. Women have a higher susceptibility to carcinogens in tobacco than men.
- Although cessation of smoking decreases the risk of developing lung cancer over time, it may never return to baseline levels.
- Passive smoking (proximity to cigarette smokers) increases the risk of developing lung cancer to approximately twice that of nonsmokers.
- Other influences may act in concert with smoking: miners of radioactive ores; asbestos workers; and workers exposed to dusts containing arsenic, chromium, uranium, nickel, vinyl chloride, and mustard gas. Asbestos increases the risk of lung cancer five-fold in nonsmokers. But heavy smokers exposed to asbestos have an approximately 55 times greater risk for development of lung cancer than that for non-smokers not exposed to asbestos.
- It is very likely that the mutagenic effect of carcinogens is conditioned by hereditary (genetic) factors.
Persons with specific genetic polymorphisms involving the P-450 genes have an increased capacity to metabolize pro-carcinogens derived from cigarette smoke.

Persons whose peripheral blood lymphocytes undergo chromosomal breakages after exposure to tobacco-related carcinogens.

These two groups have an increased propensity for developing lung cancer.

- The sequential changes leading to cancer have been best documented for squamous cell carcinomas, which begins with rather innocuous basal cell hyperplasia and squamous metaplasia and progress to squamous dysplasia and carcinoma in situ, before culminating in invasive cancer. Among the major histologic subtypes of lung cancer, squamous and small-cell carcinomas show the strongest association with tobacco exposure.

- Early genetic abnormalities can also be seen in the adjacent benign bronchial epithelium of persons with lung cancer, as well as in the respiratory epithelium of smokers without lung cancer, suggesting that there is “field effect.”

- A subset of adenocarcinomas, particularly those arising in non-smoking women of Far Eastern origin and young non-smokers harbor activating mutations of the epidermal growth factor receptor (EGFR). These tumors are sensitive to a class of agents that inhibit EGFR signaling. Other mutations occurring in 4% to 6% of adenocarcinomas are EML4-ALK tyrosine kinase fusion genes and c-MET tyrosine kinase gene amplifications. These abnormalities are rare but can be targeted with tyrosine kinase inhibitors. Hence, these mutations need to be tested for in adenocarcinomas so that specific targeted therapy can be administered if the tumors show the specific genetic alteration.

Clinical Course

- Carcinomas of the lung are silent, insidious lesions.
- In many cases, the tumors have already become unresectable before they produce symptoms.
- Symptoms may include chronic cough and expectoration.
- Advanced disease manifests as hoarseness, chest pain, superior vena cava syndrome, pericardial or pleural effusion, or persistent segmental atelectasis or pneumonitis.
- Tumor may present with symptoms from metastasis: spread to the brain (mental or neurologic changes), liver (hepatomegaly), or bones (pain).
- Metastasis to the adrenals is very common and may be discovered on imaging techniques during clinical staging of lung cancer; adrenal insufficiency (Addison disease) is however uncommon.
- Approximately 3% to 10% of all patients with lung cancer develop clinically overt paraneoplastic syndromes. These are symptom complexes that occur in patients with cancer and cannot be readily explained by local or distant spread of the tumor or by the elaboration of hormones not indigenous to the tissue of origin of the tumor.
Such syndromes may represent the earliest manifestation of an occult neoplasm. Sometimes these changes may be associated with significant clinical illness and may mimic metastatic disease confounding treatment.

Paraneoplastic syndromes seen in lung cancer patients include:
- Hypercalcemia caused by secretion of a parathyroid hormone–related peptide most commonly seen in squamous cell carcinoma
- Cushing syndrome (from increased production of adrenocorticotropic hormone)
- Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)
- Neuromuscular syndromes, including a myasthenic syndrome, peripheral neuropathy, and polymyositis;
- Clubbing of the fingers and hypertrophic pulmonary osteoarthropathy;
- Coagulation abnormalities, including migratory thrombophlebitis, nonbacterial endocarditis, and disseminated intravascular coagulation most commonly seen in adenocarcinoma

The remaining syndromes are more common with small cell carcinoma.

Morphology and histologic characteristics
- Simplistic classification of lung tumors is as small cell carcinoma and non-small cell carcinoma (NSCLC). Non-small cell carcinomas have many subtypes but adenocarcinoma and squamous cell carcinoma are the main subtypes.

Non-small cell carcinoma (NSCLC); subtype: Squamous cell carcinoma
- More common in men
- Strongly associated with smoking history
- Maybe associated with inappropriate PTH secretion - elevated Ca
- Majority of them arise centrally Associated with squamous metaplasia, dysplasia, carcinoma-in-situ
- Squamous differentiation is evidenced intercellular bridges or keratinization on morphology or diffuse p63/p40 on immunostains
- Local nodes involved in 70-90%
- Spreads outside the thorax, later than other histologic types
- Five year survival: 5-7.5%
- Molecular Genetics: Highest frequency of p53 mutations, other mutations include CDKN2A, PTEN, PIK3CA, NOTCH1, RB1

Non-small cell carcinoma (NSCLC); subtype: 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
o Slower growing, smaller mass but can metastasize early
o Local nodes involved in over 50%
o Five year survival: 10-12%

Subtypes of Adenocarcinoma
  o a. Acinar adenocarcinoma
  o b. Papillary adenocarcinoma
  o c. Solid adenocarcinoma
  o d. Mucinous adenocarcinoma

Several driver mutations in ADC have been described. KRAS mutations are the most common mutations described in Caucasian population (30%) and 10% in Asian population. There is no specific targeted therapy. Mutations in KRAS correlate with worse outcome. Newer studies have demonstrated mutations in EGFR and ALK genes, which have specific targeted therapy. See below for details.

Non-small cell carcinoma (NSCLC); subtype: Large cell undifferentiated carcinoma
  o Un-differentiated: No squamous or adeno differentiation by morphology OR by immunohistochemistry
  o Poor prognosis
  o Metastasize to liver, adrenal, brain
  o Five year survival: 2-3%

Small cell carcinoma
  o Also known as Oat cell carcinoma
  o Rapidly growing, high grade neuroendocrine tumor
  o Central
  o Strong association with smoking
  o Widely metastatic
  o Associated with Paraneoplastic Syndromes: ACTH, ADH
  o Rarely resectable
  o Rx: Radiotherapy and chemotherapy
  o 5-8% 2 year survival
  o 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, with necrosis
  o Molecular Genetics: Inactivation of p53 and RB in 100% of cases, losses of 3p, 4q, 5q, 13q and 15q

Bronchial Carcinoid
  o Low grade malignant neuroendocrine tumors
  o Locally invasive, rarely metastatic
  o Earlier age (40 years)
  o Often resectable and curable
  o Clinically: Carcinoid syndrome (rare)- intermittent diarrhea, flushing, and cyanosis
Further classified into
- Typical (< 2 mitoses per 2mm² and absent necrosis)
- Atypical (2-10 mitoses per 2mm² 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

**Therapy and Targeted therapy**

- Overall, NSCLCs carry a better prognosis than SCLCs. SCLCs have invariably spread by the time they are first detected, even if the primary tumor appears small and localized. Thus, surgical resection is not a viable treatment. These tend to be sensitive to chemotherapy but invariably recur. Median survival even with treatment is 1 year.
- On the other hand, if NSCLCs (squamous cell carcinomas or adenocarcinomas) are detected before metastasis or local spread, cure is possible by lobectomy or pneumonectomy.
- Advanced NSCLC are typically treated by radiotherapy or chemotherapy or combination of both with or without surgery.
- Failure to control NSCLC by surgical resection is associated with a miserable prognosis as these group of tumors respond poorly to conventional chemotherapy. The 5-year survival rate with even limited (less than 3 cm), localized stage I disease is only 5% in the presence of distant metastases, less than 1% of patients survive to 5 years.
- However, newer studies have shown that specific subsets of NSCLCs carry specific oncogenic mutations in potentially targetable molecules. Approximately, 10% of adenocarcinomas in non-Asian persons (and roughly 50% of adenocarcinomas in Asian populations) express constitutively activating mutations in epidermal growth factor receptor (EGFR). EGFR is upstream of the mitogen-activated protein (MAP) kinase, Akt, and Janus kinase pathways, and activation leads to augmented cell proliferation.
  - These mutations have higher incidence in women, especially non-smokers. Patients who harbor these activating mutations in EGFR respond better to anti-EGFR tyrosine kinase inhibitors such as gefitinib or erlotinib than to conventional chemotherapy.
  - Another, non-overlapping subset of adenocarcinomas (roughly 5%) have acquired a mutant fusion protein (EML-ALK) that combines portions of the echinoderm microtubule-associated protein-like 4 (EML4) and anaplastic lymphoma kinase (ALK) molecules. The resultant chimeric protein is a constitutively activated kinase that drives cellular proliferation along MAP kinase pathways. Of importance, the kinase inhibitor crizotinib significantly improves patient survival when tumors contain the EML-ALK fusion protein.
If the pathologist can identify mutant EGFR (by polymerase chain reaction techniques), or EML-ALK fusion rearrangement (by fluorescence in situ hybridization [FISH]), the oncologist now has targeted therapy in his armamentarium to handle these deadly tumors.

PD-1 (Programmed Death Receptor 1) and PDL1 (Programmed Death Ligand 1) are the new kids on the block. These form suitable targets for immunotherapy.

**PLEURAL LESIONS**

Pleural effusion: Fluid in pleural space

- Hydrothorax: Transudate, e.g., in congestive heart failure
- Pleuritis or pleural exudate:
  - i) Infection, bacterial
  - ii) Malignancy
  - iii) Pulmonary infarction
  - iv) Viral infection

Pneumothorax: Air in pleural space

Hemothorax: Whole blood in pleural space

Chylothorax: Lymphatic fluid in pleural space

Determination of transudate versus exudate source of pleural effusion

Fluid is exudate if one of the following Light’s criteria is present:

- Effusion protein/serum protein ratio greater than 0.5
- Effusion lactate dehydrogenase (LDH)/serum LDH ratio greater than 0.6
- Effusion LDH level greater than two-thirds the upper limit of the laboratory's reference range of serum LDH

**Pleural Tumors**

- “Benign,” Solitary fibrous tumor
- Direct spread of lung tumors
- Mesothelioma
- Metastasis

**Mesothelioma**

- Uncommon tumor arising from mesothelial cells
- Spreads widely in pleural space invasive by contiguous spread or diffuse seeding of pleural space
- Related to asbestos
  - 2-10% of heavily exposed pts develop mesothelioma in 20-50 year
- Presents with recurrent pleural effusion, chest pain and dyspnea
- Poor prognosis: Survival > 1 year is rare
- Cytogenetics: Deletions in chromosomes 1p, 3p, 6q, 9p, or 22q
  - Somatic mutations of tumor suppressor genes
- p16/CDKN2A : on 9p21 (used for diagnostic testing)
- NF2 : on 22q12
  - Mesothelioma- Histologic types: Epithelioid (most common), Sarcomatoid and Mixed/Biphasic