LUNG PATHOLOGY

Dr. Sofia Zilber
PULMONARY INFECTIONS
PNEUMONIA – any infection of the lung parenchyma.

(although this term is used for many interstitial non infectious lung diseases).
Defense mechanisms

Upper airways – nasal clearance
Trachea, bronchi – mucociliary clearing
Lungs - alveolar macrophages
Immune system: immunoglobulins, cell-mediated immunity
One type of pneumonia predisposes another (the most common cause of death in viral influenza epidemics is bacterial pneumonia).

The portal of entry for most pneumonias is the respiratory tract. Hematogenous spread from other organs can occur. Many patients with chronic diseases acquire terminal pneumonia while hospitalized (nosocomial infection).
Classification of pneumonia

• By specific etiologic agent
• By the clinical setting in which the infection occurs
Morphology of bacterial pneumonia

- Lobar pneumonia
- Lobular pneumonia (bronchopneumonia)

The patterns overlap!
Lobar pneumonia

- Fibrino-suppurative consolidation of a large portion of a lobe or an entire lobe.
Lobar pneumonia stages

- Congestion
- Red hepatization
- Gray hepatization
- Resolution
Congestion - vascular engorgement, few neutrophils and bacteria in alveoli.

Red hepatization – massive exudation with red cells, neutrophils and fibrin.

Gray hepatization – disintegration of RBC, fibrinosuppurative exudate.

Resolution – progressive enzymatic digestion of exudate.
Bronchopneumonia

Patchy consolidation of the lungs (areas of acute suppurative inflammation)

- May be patchy through one lobe but more often multilobar, bilateral and basal.

Micro: Suppurative inflammation in bronchi, bronchioles and alveoli.
Bronchopneumonia

Patchy area of alveoli are filled with inflammatory cells. The alveolar structure is still maintained, which is why a pneumonia often resolves with minimal residual destruction or damage to the lung.
Bronchopneumonia
Complications of pneumonia

- Abscess formation (Klebsiella, pneumococci)
- Empyema
- Organization of the exudate
- Bacteremic dissemination
Pleuritis

The pleural surface demonstrates areas of yellow-tan purulent exudate. (Pleuritis).
Organization of the exudate
Morphology of atypical pneumonia

- Interstitial inflammatory infiltrate composed of mononuclear cells and sometimes neutrophils.
- Intraalveolar proteinaceous material and hyaline membranes, reflecting alveolar wall damage (DAD).
- Viral pneumonias - necrosis of bronchial and alveolar epithelium and cytopathic changes.
Atypical pneumonia

Viral pneumonia with interstitial lymphocytic infiltrates. Note that there is no alveolar exudate.
Interstitial pneumonia
Nosocomial (hospital-acquired) pneumonia

- Gram-negative rods (Klebsiella, Enterobacter, Pseudomonas)
- Staphylococcus aureus (usually penicillin-resistant)
- Common in patients with severe underlying disease.
Aspiration pneumonia

- Occurs in markedly debilitated patients.
- Partly chemical, partly bacterial, from the oral flora:
  - anaerobic – Bacteroides, Fusobacterium, Peptostreptococcus;
  - aerobic – Streptococcus pneumonia, Staphylococcus aureus Haemophilis influenzae and Pseudomonas aeruginosa.
Aspiration pneumonia

- Necrotizing pneumonia
- Fulminate clinical course
- Common complication - lung abscess formation

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Lung Abscess

Local suppurative process with necrosis of lung tissue.

Causative organisms: aerobic and anaerobic streptococci, Staphylococcus aureus, gram-negative organisms and anaerobes from the oral cavity.
Lung Abscess mechanisms of development

- Aspiration of infective materials and gastric contents.
- Antecedent primary bacterial infections.
- Septic embolism.
- Neoplasia (secondary obstruction)
- Lung trauma and spread of infections from a neighboring organs.
- Primary cryptogenic lung abscess
Lung abscess
Lung abscess morphology

- Aspiration abscess - Rt side and single
- Abscess due to pneumonia and bronchiectases multiple, basal.
- Septic – haphazard, multiple.
- Suppurative destruction of lung within the central area of cavitation!
Chronic Pneumonia

A localized lesion in immunocompetent patient.

Causative agents:
- Nocardia
- Actinomycetes
- Histoplasma capsulatum
- Coccidoides immitis
- Blastomyces dermatitidis
- Mycobacterium (discussed separately)

Morphology – granulomatous inflammation
Pneumonia in the immunocompromised host

- CMV
- Pneumocystis carinii
- Mycobacterium avium intracellulare
- Invasive aspergillosis
- Invasive candidiasis
- “Usual” bacterial, viral and fungal organisms
Pneumocystis carinii

- Occurs predominantly in immunosuppressed persons.
- Pneumocystis is a FUNGUS!
- Clinically – fever, dyspnea and dry cough progressing to respiratory failure.
- Radiologically – bilateral alveolar and interstitial infiltrates radiating from the hilus.
- Diagnosis – BAL and lung biopsy
PCP morphology

- Foamy intraalveolar exudate
- Interstitial pneumonia
- Diffuse Alveolar Damage (DAD)
Identification of organisms

**GMS** (Gomory methenamine silver) stain highlights cysts containing sporozoites and free trophozoites. Cysts – 4-6µm in diameter with one or two dots.

Monoclonal antibodies to pneumocystis.

In situ hybridization and PCR.
CMV (β-group herpesvirus)

CMV infects and remains latent in WBC and can be reactivated when immune status is depressed.

The major envelop glycoprotein of CMV binds to EGFR.

CMV pneumonia clinical features: fever, dyspnea, nonproductive cough, diffuse chest infiltrates.
CMV morphology

- Focal or diffuse interstitial pneumonia
- Enlargement of infected cells; epithelial and endothelial cells are involved.
- Intranuclear inclusions surrounded by clear halo. In some cells - cytoplasmic inclusions (basophilic granules).

Virus identification: immunohistochemistry, PCR.
CMV pneumonia
Aspergillosis

Second most common fungal pathogen after Candida.

Septate hypae branched at 45 ° angle
Patterns of pulmonary aspergillosis:

Colonisation
Fungus ball
Hypersensitivity reaction
Allergic bronchopulmonary aspergillosis
Eosinophilic pneumonia
Hypersensitivity pneumonitis
Invasive (in immunosuppressed)
Acute invasive aspergillosis
Chronic necrotizing pneumonia

(usually angiocentric, produce infarcts)
TUBERCULOSIS
Mycobacteria

Slender aerobic rods growing in straight or branching chains.

*Mycobacterium* have a waxy cell wall composed of mycolic acid which makes them **acid fast** - they retain stains on treatment with a mixture acid and alcohol - Ziehl –Neelsen stain.

(described by two German doctors; [Franz Ziehl](https://en.wikipedia.org/wiki/Franz_Ziehl) a bacteriologist and [Friedrich Neelsen](https://en.wikipedia.org/wiki/Friedrich_Neelsen) a pathologist)
Tuberculosis epidemiology

Leading infectious case of death in the world after HIV.

- HIV makes people susceptible to TB
- Other conditions, like diabetes, renal failure, chronic lung disease, alcoholism and others increase risk of TB.

The disease affects people from low socio-economic levels
Clinical features of TB

Primary TB develops in a unsensitized person. Latent disease. Rare – progressive infection.

Secondary TB arises in a previously sensitized person. May occur:
1) shortly after primary
2) from reactivation of dormant primary lesions (most common)
3) reinfection
Primary pulmonary TB

Subpleural 1-1.5cm area • of granulomatous inflammation (Ghon focus) + hilar lymph nodes involvement = Ghon complex.

Subsequent fibrosis and • calcifications of Ghon complex.
Secondary tuberculosis

The initial lesion - focus of consolidation with variable amount of central caseation or peripheral fibrosis in apical subpleural location.

Progressive pulmonary TB – enlarged lesion with expanded caseation.

Miliary TB – up to 2 mm lesions that may coalesce.

Pleural involvement: effusion, TB empyema, obliterative fibrous pleuritis.
Secondary tuberculosis

Endobronchial, endotracheal, laryngeal TB.

Systemic miliary TB

Isolated-organ TB (meningies, kidneys, adrenals, bones, fallopian tubes etc.
Vertebral TB - Pott’s dis. Paraspinal “cold abscesses”)

Lymphadenitis ( “scrofula”) 

Intestinal TB
Morphology of secondary TB

Cavitation in upper lobes

Miliary TB of the spleen
Lung tuberculosis
Histology

- Necrotizing granuloma
- Non-Necrotizing granuloma
- Necrotizing granuloma
- Mycobacteria on ZN stain
OBSTRUCTIVE AND RESTRICTIVE LUNG DISEASES
Obstructive diseases

Characterized by an increase in resistance to airflow due to partial or complete obstruction at any level, from the trachea to the terminal and respiratory bronchioles.
CHRONIC OBSTUCTIVE PULMONARY DISEASE

- EMPHYSEMA
- CHRONIC BRONCHITIS
- BRONCHIAL ASTHMA
- BRONCHIECTASES
EMPHYSEMA
‘Emphysema is a condition of the lung characterized by abnormal, permanent enlargement of the airspaces distal to the terminal bronchioles, accompanied by destruction of their walls and without obvious fibrosis.’
CENTRIACINAR

(CENTRILOBULAR) EMPHYSEMA
Centriacinar emphysema

- Occurs predominantly in heavy smokers
- Central portion of the acini is affected
- The lesion more severe in the upper lobes
- Black pigment is present in the walls of the emphysematous space
- Inflammation around bronchi and bronchioles is common
Emphysema centriacinar, severe
PANACINAR (PANLOBULAR) EMPHYSEMA
Panacinar emphysema

- Occurs more commonly in the lower zones and in the anterior margins of the lungs
- The acini are uniformly enlarged
- Associated with $\alpha_1$-antitrypsin deficiency
α1-Antitrypsin Deficiency

- Abnormally low serum level of protease inhibitor (Pi)

  Genetics: gene for α1-antitrypsin (chromosome 14) is very polymorphic and at least 75 forms of protein have been identified.

  PiMM is the most common form.

  PiZZ – only 10% of circulating protein.

  Risk of clinical disease.
A. Centrilobular emphysema  
B. Panlobular emphysema
DISTAL ACINAR (PARASEPTAL) EMPHYSEMA
Paraseptal emphysema

- Upper parts of the lungs are more severely affected
- Involves the lung tissue adjacent to the pleura, along the lobular connective tissue and at the margins of the lobules
- Occurs adjacent to areas of fibrosis, scarring, atelectasis
- Spontaneous pneumothorax in young adults
Other types of emphysema
Bullous emphysema

Any form of emphysema that produces large subpleural spaces more than 1 cm in diameter

Most often subpleural and occurs near the apex

Rupture of bullae leads to pneumothorax
CHRONIC BRONCHITIS
+
BRONCHIOLITIS
Chronic bronchitis

- Persistent cough and sputum production for at least 3 months in at least 2 consecutive years

  - Simple chronic bronchitis –
  - Chronic asthmatic bronchitis (+airways – hyperreactivity)
  - Chronic obstructive bronchitis (+airflow – obstruction and emphysema)
CHRONIC BRONCHITIS PATHOGENESIS

- Initiating factor – chronic irritation (tobacco smoke, inorganic dusts. 90% of patients are smokers)
  - Bacterial and viral infections are triggers of acute exacerbation.
  - The earliest feature of chronic bronchitis is hypersecretion of mucus.
  - Accompanying alteration in the small airways – BRONCHIOLITIS - can result in earlier manifestation of chronic obstruction
Macro: hyperemia and edema of mucous membranes with excessive mucous or mucopurulent secretion

Micro: 

Chronic inflammation

Enlargement of mucus-secreting glands of trachea and bronchi

Increased number of goblet cells

Squamous metaplasia and dysplasia of bronchial epithelium

Narrowing of bronchioles by mucous plugging, inflammation and fibrosis up to bronchiolitis obliterans
BRONCHIAL ASTHMA
Asthma is a chronic inflammatory disorder of the airways that causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough. These symptoms are associated with bronchoconstriction and airflow limitation that are at least partially reversible.
BRONCHIAL ASTHMA

ATOPIC • Evidence of allergic sensitization in patients with history of other allergic symptoms

NON-ATOPIC • Without evidence of allergic sensitization

Bronchospasm can be triggered by diverse mechanisms: infections, irritants, exercise
ATOPIC ASTHMA

Classic example of type I IgE-mediated hypersensitivity reaction

Usually begins in childhood

Triggered by environmental allergens (dusts, pollens, food etc)

Positive family history of asthma is common

Positive skin tests
NON-ATOPIC ASTHMA

No evidence of allergic sensitization
Viral respiratory infections are common triggers
Hyperirritability of the bronchial tree
Virus-induced inflammation of the respiratory mucosa lowers the threshold of the subepithelial vagal receptors to irritants
Aspirin-sensitive asthma occurs in individuals with recurrent rhinitis and nasal polyps.

Sensitivity to small doses of aspirin.

Aspirin inhibits the cyclooxygenase pathway of arachidonic acid metabolism without affecting the lipooxygenase pathway → ↑ leucotrienes → bronchoconstriction.
Morphology

Mucous plugs with Curschmann spirals and Charcot-Leyden crystals

Basement membrane thickening

Inflammation and edema of bronchial wall

Increase in size of the submucosal glands

Bronchial smooth muscle hypertrophy
MUCOUS PLUGS
CHARCOT LEYDEN CRYSTALS
COLOR FIGURE 3-1. In Curschmann spiral, the dark-staining core of inspissated mucus is surrounded by lighter mucus. (Papanicolaou stain; oil immersion.)
BASEMENT MEMBRANE THICKENING
SMOOTH MUSCLE HYPERTROPHY
HYPERTROPHY OF SUBMUCOSAL GLANDS
BRONCHIECTASIS
Bronchiectasis is a disease characterized by permanent dilation of bronchi and bronchioles caused by destruction of the muscle and elastic tissue, resulting from or associated with chronic necrotizing infections.
Etiology and pathogenesis

Postinfectious conditions (necrotizing pneumonia)

Congenital conditions (cystic fibrosis, intralobular sequestration, ciliary dyskinesia and Kartagener syndrome, immunodeficiency)

Bronchial obstruction (tumor, foreign bodies, mucus)

Others (Rheumatoid arthritis, SLE, IBD, GVHD)
Morphology

Bilateral lower lobes involvement •
Airways dilatation: cylindrical, fusiform, saccular
Intense acute and chronic inflammation. •
Necrosis. Lung abscess formation
BRONCHECTASIS LOCALIZED
Diffuse interstitial lung diseases
Diffuse Interstitial (Infiltrative, Restrictive) Diseases

Characterized by reduced expansion of lung parenchyma with decreased total lung capacity
Diffuse Interstitial (Infiltrative, Restrictive) Diseases

- Heterogeneous group of disorders characterized predominantly by diffuse and usually chronic involvement of the pulmonary connective tissue, principally the most peripheral and delicate interstitium in the alveolar walls.
Idiopathic pulmonary fibrosis
Pathogenesis

“Repeated cycles” of alveolitis
Healing with exuberant fibroblastic proliferation (mediator TGF-β)
Morphology

**Macro:**
- Lower lobes – predominance
- Cobblestone – pleural surface
- Cut surface: – firm, rubbery, white areas (fibrosis) in subpleural areas and along the interlobular septa

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Microscopically: usual interstitial pneumonia (UIP)

- Patchy interstitial fibrosis
- Fibroblastic foci
- Honeycomb fibrosis
- Temporal heterogeneity
- Hyperplasia of type II pneumocytes
- Mild to moderate inflammation
- Smooth muscle hyperplasia
- Intimal fibrosis and medial thickening of pulmonary arteries
Fibroblastic foci
Interstitial fibrosis
Honeycombing
Bronchiolitis obliterans organizing pneumonia (BOOP)
Characteristics

Unknown etiology •
Cough and dyspnea •
Radiologically: subpleural or peribronchial patchy areas of airspace consolidation •
Spontaneous recovering or treatment with oral steroids for 6 months •
Polypoid plugs of loose connective tissue within alveolar ducts, alveoli, bronchioles
Sarcoidosis

Systemic disease of unknown cause characterized by noncaseating granulomas in many tissues

- Women > Men
- Black > White

Histologic diagnosis by exclusion!

Variable clinical course; 90% of patients have hilar lymphadenopathy + lung involvement
Asteroid body

Schaumann body

Schaumann body

Schaumann body, polarization
Environmental and occupational diseases
Hypersensitivity pneumonitis (allergic alveolitis)

Spectrum of immunologically mediated predominantly interstitial lung disorders
Abnormal sensitivity to antigen, which involves alveoli (in contrast to asthma)
Acute attack (4-6 hours after exposure): fever, dyspnea, cough, leukocytosis
Chronic disease – progressive respiratory failure.
Removal of the causative agent prevents transition to fibrosis
<table>
<thead>
<tr>
<th>Antigen</th>
<th>Source</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thermophilic bacteria</strong></td>
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<tr>
<td><em>Micropolyspora faeni</em></td>
<td>Moldy hay</td>
<td>Farmer’s lung</td>
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<tr>
<td><em>Thermoactinomyces vulgaris</em></td>
<td>Moldy compost</td>
<td>Mushroom worker’s disease</td>
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<tr>
<td><em>Thermoactinomyces saccharii</em></td>
<td>Moldy sugar cane</td>
<td>Bagassosis</td>
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<tr>
<td><em>Thermoactinomyces vulgaris</em></td>
<td>Air conditioners, humidifiers</td>
<td>Air conditioner lung/humidifier lung</td>
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<tr>
<td><em>Thermoactinomyces candidus</em></td>
<td>Air conditioners, humidifiers</td>
<td>Air conditioner lung/humidifier lung</td>
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<tr>
<td><strong>Molds</strong></td>
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<tr>
<td><em>Cryptostroma corticale</em></td>
<td>Moldy maple bark</td>
<td>Maple bark stripper’s disease</td>
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<tr>
<td><em>Aspergillus clavatus</em></td>
<td>Moldy barley</td>
<td>Malt worker’s lung</td>
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<tr>
<td><em>Graphium spp.</em></td>
<td>Moldy wood dust</td>
<td>Sequoiosis</td>
</tr>
<tr>
<td><em>Pullularia spp.</em></td>
<td>Moldy wood dust</td>
<td>Sequoiosis</td>
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<tr>
<td><em>Trichosporon cutaneum</em></td>
<td>Home environment</td>
<td>Summer-type hypersensitivity pneumonitis (Japan)</td>
</tr>
<tr>
<td><strong>Other bacteria</strong></td>
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<tr>
<td><em>Bacillus subtilis</em></td>
<td>Water</td>
<td>Detergent worker’s lung</td>
</tr>
<tr>
<td><em>Bacillus cereus</em></td>
<td>Water</td>
<td>Humidifier lung</td>
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<tr>
<td><strong>Bacterial products</strong></td>
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<td></td>
<td>Cotton</td>
<td>Byssinosis</td>
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<tr>
<td><strong>Amoebi</strong></td>
<td>Water</td>
<td>Humidifier lung</td>
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<tr>
<td><strong>Insect products</strong></td>
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<tr>
<td></td>
<td>Grain</td>
<td>Wheat weevil disease</td>
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<tr>
<td><strong>Chemicals</strong></td>
<td></td>
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<tr>
<td>Trimellitic anhydride (TMA)</td>
<td>Plastics, rubber manufacturing</td>
<td>Chemical worker’s lung</td>
</tr>
<tr>
<td>Methylene diisocyanate (MDI)</td>
<td>Plastics, rubber manufacturing</td>
<td>Chemical worker’s lung</td>
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<tr>
<td>Toluene diisocyanate (TDI)</td>
<td>Plastics, rubber manufacturing</td>
<td>Chemical worker’s lung</td>
</tr>
<tr>
<td>Pyromellitic dianhydride (PMDA)</td>
<td>Epoxy resin</td>
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</tbody>
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Source: from Katzenstein and Askin,1 p 139, with permission.
Drug- Induced pulmonary diseases
Table 15-7. Examples of Drug-Induced Pulmonary Disease

<table>
<thead>
<tr>
<th>Drug</th>
<th>Pulmonary Disease</th>
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</thead>
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<tr>
<td>Cytotoxic drugs</td>
<td></td>
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<tr>
<td>Bleomycin</td>
<td>Pneumonitis and fibrosis</td>
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<tr>
<td>Methotrexate</td>
<td>Hypersensitivity pneumonitis</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Pneumonitis and fibrosis</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>Hypersensitivity pneumonitis</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Bronchospasm</td>
</tr>
<tr>
<td>β-Antagonists</td>
<td>Bronchospasm</td>
</tr>
</tbody>
</table>
Acute lung injury

Acute respiratory distress syndrome (ARDS)

Diffuse alveolar damage (DAD)
- morphologic equivalent
Acute respiratory distress syndrome

- Rapid onset of severe life threatened respiratory insufficiency, refractory to oxygen therapy
- Complication of numerous conditions
- Radiologically: diffuse alveolar infiltration
Causes of ARDS

- Sepsis*
- Diffuse pulmonary infections*
- Gastric aspiration*
- Mechanical trauma (including head injuries)*
- Inhaled irritants, smoke, oxygen
- Narcotics or barbiturate overdose
- Hypersensitivity reactions
- Others
Pathogenesis

Damage to the alveolar capillary membrane (including microvascular endothelium and alveolar epithelium) →
↑vascular permeability, alveolar flooding, loss of diffusion capacity and surfactant abnormality (due to damage to pneumocytes) → hyaline membranes

Neutrophiles play an important role

Coagulation system dysregulation
Morphology

Acute phase

- Congestion, edema
- Inflammation
- Fibrin deposition
- Hyaline membranes!

Organizing phase:

- Organization of the fibrin exudate
- Thickening of alveolar septa
- Type II cells hyperplasia
DAD

Macro: heavy, firm, red lung
DAD – Early exudative phase

Hyaline membranes
ORGANIZING PHASE

Type II cells hyperplasia
DAD – Fibroblastic proliferation

Airspace organization
LUNG TUMORS
Carcinomas – 90-95% •
Bronchial carcinoids – 5% •
Mesenchymal tumors and others – 2-5%
Lung cancer incidence

Most common cause of cancer mortality worldwide

Occurs between 40 and 70 years, peak in the fifties or sixties.

2% before age 40

5-year survival rate 16%
Lung cancer etiology and pathogenesis
Tobacco smoking

- average smokers – 10-fold greater risk
- heavy smokers – 60-fold greater risk
- women have a higher susceptibility to carcinogens than men do
- cessation of smoking for 10 years reduces risk but never to control levels
Industrial hazards

High-dose ionizing radiation •
Uranium •
Asbestos (asbestos + smoking = 50-90 times greater risk)

Air pollutions

Atmospheric pollutants •
Radon •
Classification (WHO)

- Squamous cell carcinoma
- Adenocarcinoma
  - Acinar, papillary, bronchioloalveolar, solid, mixed
- Large cell carcinoma
- Adenosquamous carcinoma
- Pleomorphic, sarcomatoid carcinoma
- Small cell carcinoma
- Large cell neuroendocrine carcinoma
- Carcinoid tumor (typical, atypical)
- Carcinomas of salivary gland type
- Unclassified carcinoma
Clinically important:

Small cell carcinoma •
most often metastatic, high initial response to chemotherapy

Non- small cell carcinoma •
less often metastatic, less responsive
Pathology

- 75% - area of lung hilus
- Small number – on periphery
  (adenocarcinoma)
- Distant spread occurs by lymphatic and hematogenous pathways

*adenocarcinoma metastasize at an early stage*
*SCC metastasize outside the thorax late*
Sites of metastases:

- Adrenal – more than half of the cases
- Liver – 30-50%
- Brain – 20%
- Bones – 20%
Squamous cell carcinoma

- Men > Women
- Closely correlated with smoking history
- Most SCC arise centrally
- Squamous metaplasia and dysplasia are often seen
Well-differentiated squamous carcinoma, with keratinization.
Poorly differentiated squamous cell carcinoma

**Immunophenotype:**
- P63 +
- High molecular weight keratins +
- Cytokeratin 7 –
- TTF1 -
Adenocarcinoma

Most common type of lung cancer in women and nonsmokers
(still, 75% are found in smokers)
Smaller than SCC and peripherally located, often central scar
Grows more slowly than SCC, but metastasize widely and earlier
Immunophenotype:

TTF1 +
Cytokeratin 7 +
Cytokeratin 20 -
P 63 -
Bronchioloalveolar carcinoma

- Peripheral portion of the lung as single nodule or in pneumonia-like consolidation

  Histologically – no evidence of stromal, vascular or pleural invasion

  Growth along preexisting structures without destruction of alveolar architecture ("lepidic" growth)
BAC, nonmucinous type

- Peripheral lung nodule
- No aerogenous spread
- Amenable to surgical resection
BAC, nonmucinous type
BAC, mucinous type

- Aerogenous spread
- Solitary nodule
- Multiple nodules
- Pseudopneumonic consolidation
- Less likely to be cured by surgery
BAC, mucinous type
Small cell carcinoma

The most aggressive lung tumor

- Occurs both in major bronchi (predominantly) and on the periphery
- Strongly associated with cigarette smoking
Small cell carcinoma
"Azzopardi phenomenon"
Large cell carcinoma

Undifferentiated carcinoma that lacks the cytological features of small cell carcinoma and glandular or squamous differentiation.

On EM – minimal glandular or squamous differentiation is common

Large cell neuroendocrine carcinoma has the same molecular changes as small cell carcinoma
Staging

T1- tumor <3 cm without pleural or main stem bronchus involvement

T2- tumor 3-7 cm or involvement of main stem bronchus 2 cm from carina, visceral pleura or lobar atelectasis

T3- tum. >7 cm or with involvement of chest wall, diaphragm, mediastinal pleura, pericardium, main stem bronchus 2 cm from carina, or entire lung atelectasis

T4- invasion of mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina or separate tumor nodules in different ipsilateral lobe.
Prognosis

Overall 5-year survival rate is 15%

For localized cases 48% survival rate

Adenocarcinoma and squamous cell ca tend to remain localized longer and have a slightly better prognosis than undifferentiated ca.

Small cell ca – resection is ineffective.

Particular sensitivity to radio and chemotherapy. Mean survival $\approx 1$ year
Neuroendocrine proliferations and tumors

- Tumorlets
- Carcinoids – typical – atypical
- Small cell carcinoma
- Large cell neuroendocrine carcinoma
Tumorlet

Benign neuroendocrine cell proliferation, resembles carcinoid

The size is no more than 4 mm

Occur within and around the bronchovascular sheaths

May occur with or without associated lung disease
Carcinoid tumorlet
Carcinoid Tumors

Central or peripheral mass • Most are intraluminal tumor, some infiltrate the lung parenchyma

Diameter – 3-4 cm
Bronchial carcinoid
Characteristic growth patterns in neuroendocrine tumors
Typical carcinoid

Less than 2 mitoses per 10 HPF •
No necrosis •

Atypical carcinoid

2-10 mitoses per 10 HPF •
Foci of necrosis •
More atypia, cellularity, lymphatic invasion •
Clinical presentation

Intraluminal growth → cough, hemoptysis, secondary infection, bronchiectasis, emphysema, atelectasis.

Secretory activity → carcinoid syndrome (intermittent attacks of diarrhea, flushing and cyanosis)

Most carcinoids have relatively benign course. (Low grade malignancy).
Can occur in patient with MEN 1.
5-year survival:

- Typical carcinoid - 87%
- Atypical carcinoid – 56%
- Large cell neurondocrine ca – 27%
- Small cell carcinoma – 9%
Other lung tumors

Mesenchymal: hemangioma, hemangiopericytoma, inflammatory myofibroblastic tumor, leiomyoma, leiomyosarcoma

Hematopoietic: non-Hodgkin and Hodgkin lymphoma, Langerhans cell histiocytosis

Hamartoma
Lung hamartoma

A hamartoma is a lesion in an organ that is composed of tissue elements normally found at that site, but growing in a haphazard mass.

Relatively common lesion
- Peripheral solid nodule 3-4 cm, well circumscribed

Microscopically: nodules of mesenchymal tissue (cartilage, fat, fibrous tissue) intersected by epithelial clefts.
Some features indicate that lung hamartoma is neoplasm, rather than a congenital lesion:

- rarity in childhood
- increasing incidence with age
- chromosomal aberrations
Metastatic tumors

- Multiple discrete nodules (mostly on periphery)
- Solitary nodule
- Endobronchial
- Pleural
- “Lepidic” growth, similar to BAC
- Growth in peribronchiolar and perivascular tissue spaces
- Diffuse intralymphatic dissemination
Metastatic carcinoma
Immunohistochemistry helps to find the tumor origin:

cytokeratin 7, TTF1 – lung

cytokeratin 20, CDX2 – colon

PSA, PAP – prostate

thyroglobulin – thyroid

ER, PR – breast, female genital tract
PLEURAL TUMORS
Malignant pleural tumors

Primary

Secondary - more common! (most common origins - lung and breast)
Malignant mesothelioma

- Asbestos exposure related
- Long latent period – 25-40 years
- Risk for mesothelioma is not magnified by smoking (in contrast to carcinoma)
Malignant mesothelioma morphology

Diffuse spread in the pleura associated with extensive pleural effusion

- Epithelioid type
- Sarcomatous type
- Mixed
Malignant mesothelioma.

Note the thick, firm, white pleural tumor tissue that ensheathes this bisected lung.
Malignant mesothelioma, epithelial type

Malignant mesothelioma, mixed type
Immunohistochemistry of MM

- Calretinin +
- WT 1 +
- Thrombomodulin +
- Keratin 5/6 +
- CEA –
- TTF1 –

Different epithelial markers -
Clinical course

- Recurrent pleural effusion
- Chest pain, dyspnea
- 50% die within 12 months
- Some improvement with aggressive therapy (extrapleural pneumonectomy, chemotherapy, radiation)
Solitary fibrous tumor

- Soft tissue tumor, occurs in pleura and other sites
- Often is attached to the pleura by pedicle
- Do not produce pleural effusion
- Microscopically: whorls of reticulin and collagen fibers and interspersed spindle cells
- Immunohistochemistry: CD 34+
Solitary fibrous tumor, criteria of malignancy

- Large size (> 10 cm)
- Pleomorphism
- Necrosis
- Mitotic activity (> 4 mitoses for 10 HPF)
Dr. Sofia Zilber