Restrictive:

Restrictive Overview

Physiology

Can't get air in, but can exhale normally

normal FEV1/FVC

↓ TLC: hallmark is TLC < 80% of predicted

diffusing capacity often reduced w/parenchymal disease

Acute (ARDS) vs. Chronic presentations

Alveolar macrophage plays central role in chronic restrictive diseases: controls deposition of collagen/fibrosis

not all chronic restrictive diseases are due to fibrosis (amyloid/malignancy)

Extra-Parenchymal (outside of lung) Restrictive diseases

Etiology:

Impaired muscle function

ALS, MG, guillain-Barre, polio, etc….

Chest wall disease

obesity, kyphoscoliosis, severe burns, etc….

"Other" etiology

pneumothorax, pleural effusions, complete obstruction to major bronchus

Physiology

Whatever the etiology, lung parenchyma is normal

The A-a gradient will be normal

ARDS = DAD

Pathogenesis

An acute problem!

sysemic insult: sepsis, trauma, shock, DIC, etc

injury (immune/cytokine) to alveolar capillaries: ↑ permeability

eosinophilic edema fluid in alveoli

hyaline membrane forms around alveoli

gas exchange impaired

Pathologic changes: 3 phases

Exudative: edema & hemorrhage

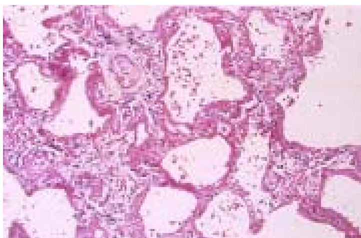
4-7 days after onset of respiratory failure

gross: focally hemorrhagic, airless, heavy lungs, solid

histologically: Eosinophilic hyaline membranes, capillary congestion

Hyaline membranes are da bomb

made of fibrin, cellular debris, and leaked serum proteins



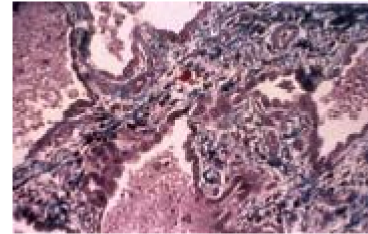
Proliferative: organization & repair

1-3 weeks

gross: lungs are rigid, red, heavy

histologically: hyperplastic type 2 cells

cuboidal type II pneumocytes widen alveolar wall



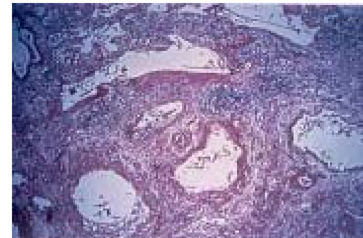
Fibrotic: end stage fibrosis

3-4 weeks +

lung now remodelled

gross: fibrosis/cysts

histology: fibrotic microcysts represent progression of ring shaped alveolar duct fibrosis, alveolar walls widened by collagen/scarring



Prognosis

correlates with duration of injury, not nature of injury

2/3 of survivors have abnormal pulmonary function afterwards

ARDS & Pulmonary Edema Syndromes

How does fluid get into the lungs?

- Summary
  - any abnormal Starling forces (except no known instance of primary increases in π(pmv) = colloid perimicrovascular)
  - MOST clinical cases of pulmonary edema are due to ↑ permeability or ↑ capillary pressure
  - cardiogenic: fluid in the lungs because of poor heart function
  - non-cardiogenic: fluid in the lungs (usually) due to lung vascular endothelium injury
- Specific:
  - $EVLW = K[(P_{MV} - P_{PMV}) - \sigma(\pi_{MV} - \pi_{PMV})] - \text{LYMPH FLOW}$
  - Variables
    - EVLW = extravascular lung water content
    - K = measure of membrane leakiness to water
    - Pmv = capillary hydrostatic pressure
    - Ppmv = interstitial hydrostatic pressure
      - pmv = perimicrovascular
    - σ = measures vascular permeability to proteins compared to water
    - πmv = osmotic pressure of capillary
    - πpmv = osmotic pressure of interstitum
  - ↑ K → ARDS
  - ↓ σ → ARDS
  - ↑ Pmv → CHF, volume overload, HTN, etc
  - ↓ Ppmv → (rare) upper airway obstruction, reexpansion pulmonary edema
  - ↓ πmv → hypoalbuminemia, nephrotic syndrome
  - ↓ lymph flow → malignancy, trauma to thoracic duct

Pathophysiology of ARDS

- permeability pulmonary edema = ARDS
  - extends beyond Edema
    - inflammation → cellular proliferation → fibrosis (pathologically called DAD)
- Hypoxemia
  - blood perfuses liquid-filled alveoli, cannot equilibrate with air
  - R → L shunt
  - vessels lost ability to vasoconstrict, so shunting can't be minimized: we don't really know why
- Compliance
  - Lungs become less compliant: restrictive defect
    - Note: this "restriction" is theoretical because you don't go around giving people with ARDS PFT's
  - Stiff lungs necessitate use of ↑ airway pressures on the vent
    - this can cause barotrauma

Clinical

- ARDS characterized by dyspnea, progressive hypoxemia, bilateral radiographic lung infiltrates, and ↓ pulmonary compliance
- mortality rate approaches 50%
- ARDS is not a disease, but it is a resonse to injury
  - Infections
    - sepsis
    - pneumona
  - Drugs
    - heroin
    - cocaine
  - Hemodynamic
    - shock
  - Trauma
    - fat emboli
    - lung contusion
    - massive blood transfusion
  - Inhaled toxins
    - oxygen!! free radical damage, can turn into DAD
    - smoke inhalation
  - Misc
    - aspiration
    - pancreatitis
- ABG's:
  - ARDS is said to exist when there is acute hypoxemic respiratory failure with large R → L shunt
  - R → L shunt defined as PaO_2/FiO_2 ratio of ≤ 200
    - PaO_2/FiO_2 ratio: multiply % FiO_2 by 7 → this is what PaO_2 should be
      - Between 200 and 300: any lung injury
      - Below 200: R → L Shunt
  - See problem set for examples (i.e. Problem set #3, case 1, problem 3)
- CXR: diffuse patchy infiltrates
- Cardiac Cath: ↓ or normal pulmonary capillary wedge pressure
  - this just proves that the L heart is normal
- Treatment
  - no role for systemic corticosteroids in early ARDS
  - vent: PEEP (positive end-expiratory pressure)
    - but this can cause barotrauma: you can't win

Restrictive:

BOOP = BO = COP = UCP

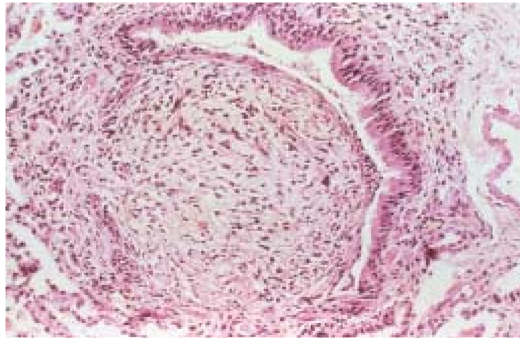
Pathogenesis

failed restoration after pneumonia

Pathology

patchy intraluminal polyps (= bronchiolitis obliterans) with central collection of macrophages, lymphocytes, and plasma cells.

polyps can block airway, causing an element of obstruction



absence of honeycombing: unlike DAD, has no microcystic change

Clinical

X-Ray: multiple nodular opacities

Steroid responsive

UIP = IPF = Kiss of Death

Pathogenesis

idiopathic, possibly immune

Pathology

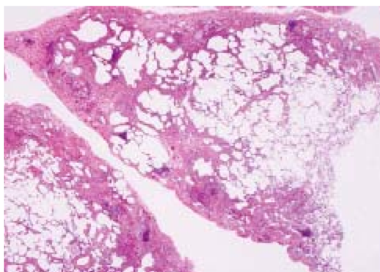
Gross: analogous to end-stage kidney

small lungs, cirrhotic, hobnailed surfaces

diffuse fibrosis with microcysts (looks just like DAD)

microcysts peripherally distributed

honeycombing (due to microcysts)/emphysema may be present



Histopathology: 3 stages, but hard to define because stages are so slow

Acute: seldom seen, indistinguishable from early DAD (edema, hyaline membranes), don't worry about it

Proliferative: interstitial/intraalveolar fibrosis

Fibrotic: can no longer recognize alveoli, architectural disorganization, collagen, microcysts.

Pathognomonic: focus of fibroblastic proliferation: manufactures collagen

Clinical

presentation

50-60 yo, M > F

insidious onset: dry cough, gradual increase in dyspnea

hypoxemia, ↓ PCO2 due to hyperventilation

note: due to insidious course, patient may not seek medical attention until they have end-stage fibrosis

PE: rapid shallow respirations, fine end-inspiratory crackles (rales) over lower lobes, digital clubbing

X-Ray: increased interstitial markings = "reticulonodular markings"

Not steroid responsive, transplant needed

PFTs: ↓ TLC, VC, RV; normal or ↑ FEV1/FVC. ↓ corected DLCO

ABGs: hypoxemia, low PaCO2 due to hyperventilation

median survival: 5 years, W > M

rate of cancer is increased, as it is in other fibrotic lung dz

Restrictive:

HSP

Pathogenesis

extrinsic allergic alveolities due to inhalation of organic dusts

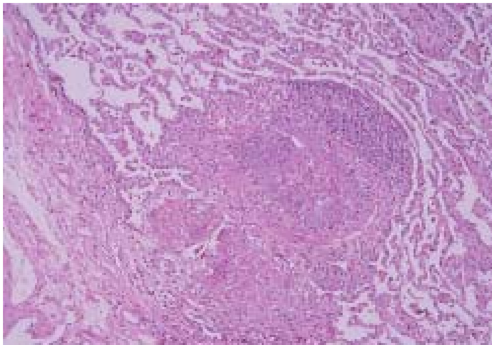
inflammation can result in parenchymal fibrosis

Pathology

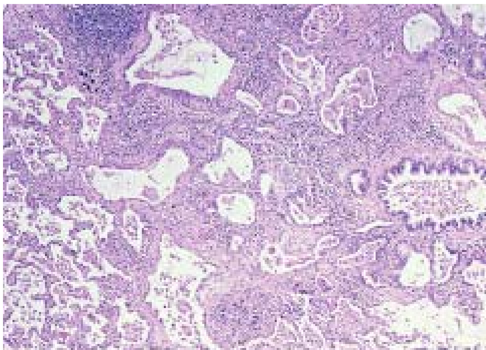
key feature: incomplete non-caseating granulomas and inflammation

diagnostic triad:

1) inflammation of bronchiole or around bronchiole (= bronchiolitis/peribronchiolotis)

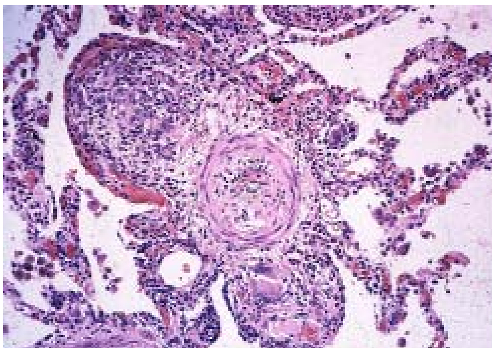


2) chronic interstitial pneumonitis



3) baby ("incomplete") granulomas = single multinucleated giant cell (at 5 oclock in picture) seen in 70% of biopsies

NOTE that sarcoid has complete granulomas



Clinical:

Responds to steroids

presents with cough, fevers, dyspnea (especially after Ag exposure)

Sarcoid

Pathogenesis

multisystem granulomatous disease

cause is a mystery

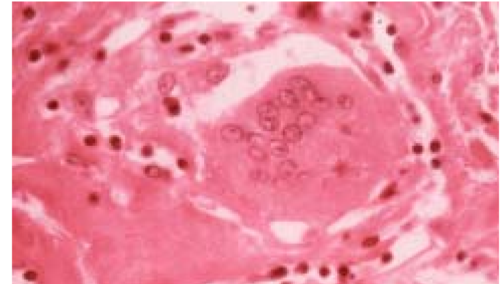
Pathology

initial lesion in lung is lymphocytic alveolitis

classic granuloma is non-caseating

involves wall of bronchioles

can follow path of lymphatics



very little fibrinoid necrosis

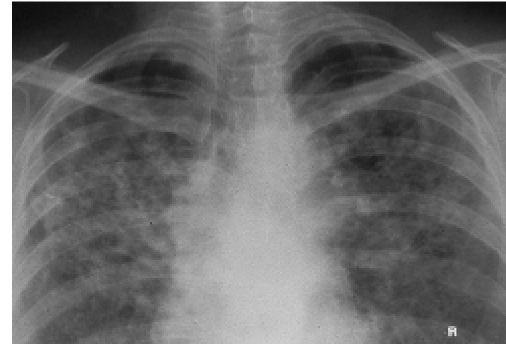
Clinical

young adults: 20-40, hilar enlargement, expanded mediastinum

biopsy to dx sarcoid vs. lymphoma

but if skin lesions present, it's sarcoid

X-Ray: bilateral enlarged hilar lymph nodes, ↑ interstitial markings



PFT: ↓ of lung volumes, ↓ diffusing capacity, hypoxemia, ↓ corrected DLCO

can also be element of obstruction if granulomatous inflammation involves airways

ABGs: hypoxemia, especially during exercise. Hypercapnia in advanced cases

Active dz: treasted w/ steroids

inactive disease: will regress or is already fibrotic

Prognosis

favorable: remove offending antigen

resolves on its own: 70%

responds to steroids: 25%

gets worse, like IPF: 5%

Obstructive:

Overview of Obstruction/COPD

- *Important determinants of airway caliber:*
  - 1) material in lumen (BOOP)
  - 2) abnormally thick mucosa (chronic bronchitis)
  - 3) abnormal tethering of airways by parenchyma
  - 4) smooth muscle contracted (asthma)
  - 5) ↑ pleural pressure (theoretical only)
- *Pathophysiology: diffuse airway obstruction*
  - ↓ FEV1/FVC ratio
  - V/Q mismatch
  - in general, patients w/airway obstruction DO RESPOND to supplemental O2
  - ↑↑ work of breathing due to hypoxemia/dyspnea/work exceeding muscle capacity
- *COPD: A group of diseases with diffuse obstruction to airflow in smaller airways especially during expiration.*
  - Most commonly, implies: Chronic bronchitis & Pulmonary Emphysema
  - Bronchial asthma also included
    - may progress to COPD, bronchiectasis, and atelectasis
  - patients often have combination of these 3 diseases

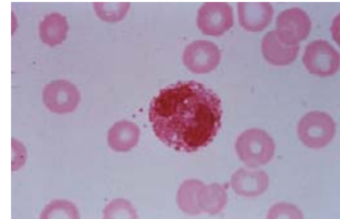
CHRONIC BRONCHITIS VERSUS EMPHYSEMA

CLINICAL FEATURE	EMPHYSEMA (PINK PUFFER, TYPE A)	CHRONIC BRONCHITIS (BLUE BLOATER, TYPE B)
Age	Older	Younger
Stature	Tall, thin	Stocky, obese
Cor pulmonale	Late in course	Early in course
Hypoxemia	Mild	Prominent
Hypercapnia	Late in course	Early in course
Lung compliance	Increased	Normal
DLCO	Reduced	Normal
Airway obstruction	Severe	Moderate
Hematocrit	Normal	Increased

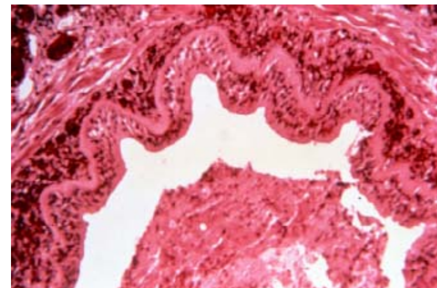
  - note that these pink/blue nicknames have fallen out of favor because most people have both even if they look blue or pink.
  - risk factor: smoking, but less than 15% of smokers get COPD, but cigs account for 90% of risk
  - Physical Exam
    - wheezing
    - prolonged expiratory phase
    - may see clubbing
    - accessory muscles of respiration w/ severe dz
  - CXR: ↓ lung markings, hyperinflation of lung
    - emphysema destroys lung tissue
  - ABG:
    - mild to moderate hypoxemia w/o hypercapnea (early dz)
    - w/ FEV1 < 1 L, hypercapnia becomes common
    - Bronchitis: preserved DLCO
    - Emphysema: low DLCO
  - Prognosis/complications
    - if a smoker quits smoking, rate of decline in lung function returns to normal rate
    - hypoxemia: pulmonary arterial vasoconstriction → rising pulmonary artery pressure
    - RV can fail → cor pulmonale
      - heart trouble due to the lung
    - bullous lesions can rupture → pneumothorax
  - Treatment
    - bronchodilators: β2 agonists
    - corticosteroids
    - antibiotics
    - Important: Home oxygen to prevent pulmonary hypertention
    - NO Sedation (Atavan)
  - Less common diseases still called "COPD"
    - bronchiectasis
    - cystic fibrosis
    - α-1-antitrypsin deficiency

Bronchial Asthma

- *Pathogenesis*
  - paroxysmal widespread narrowing of small conducting airways due to hypersensitivity of bronchial tree
  - stimulus: could be allergic
  - reversible, intermittent
  - chronic inflammatory disease: cannot be cured, but can be controlled in most patients
  - chiefly eosinophilic response



  - mast cells also play important role
- *Pathology*
  - Gross: distended lungs, may have atelectatic foci
    - small bronchi may be dilated and filled w/mucous plugs
  - Microscopic:

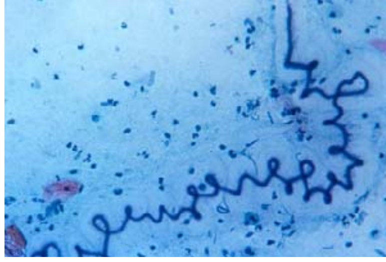


    - 1) thickened BM
    - 2) inflammation in wall
    - 3) inflammatory exudate in lumen

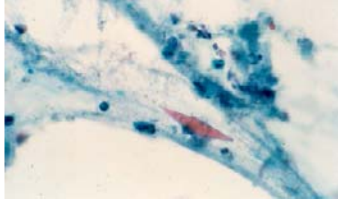
Obstructive:

Sputum:

Curschmann's spirals: curled up globs of mucus



Charcot-Leyden crystals (eosinophilic)



eosinophils & mast cells

Pathophysiology

bronchial hyperresponsiveness is hallmark

methacholine challenge

anything that triggers mast cells can trigger an acute asthma attack

Clinical

Acute airway attack (exposed to environmental agent)

this usually responds to smooth muscle relaxants

More complex problem: obstruction due to inflammation that is not fully relieved by smooth muscle relaxants

Exam:

tachypneic and distressed, wheezing, prolonged expiratory phase

ABG:

↑ A-a gradient

hypoxemia corrects w/O2 → V/Q mismatch

can also be component of shunt involved due to atelectasis

At first, $PaCO_2$ usually ↓ because central stimuli to ↑ breathing

But then, as breathing becomes more work, $PaCO_2$ rises

A normal $PaCO_2$ w/severe asthma = impending disaster

CXR: hyperinflation

used more to rule out PTX, pneumonia, etc

Treatment

systemic corticosteroids

bronchodilators

ventilation w/SEVERE obstruction

May be asymptomatic between attacks, but methecholine challenge will always be positive

Chronic Bronchitis

Definition

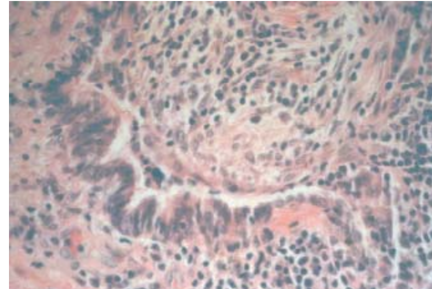
chronic productive cough of 3+ months, for not less than 2 successive years

Pathogenesis

Smoking, environmental

Pathology

can look like BOOP



REID Index: 50% or more = chronic bronchitis

normal is 33%

defined as ratio of mucosa to entire bronchial wall

non-functional cilia

goblet cell metaplasia, lots of secretions

Pathophysiology

obstruction of small airways (bronchioles mostly)

Clinical

Signs & Symptoms

chronic cough with expectoration (thick yellow sputum)

recurrent respiratory infections

hypoxia (cyanosis)

polycythemia

Obstructive:

Emphysema

Definition

enlargement of respiratory airways with associated destruction and loss of tissue

Pathogenesis

inbalance between elastases (alveolar macrophages and PMNs) and inhibition (α-1-antitrypsin) leads to lung digestion

cigarette smoking ↑↑ macrophages & polys → ↑ digestion

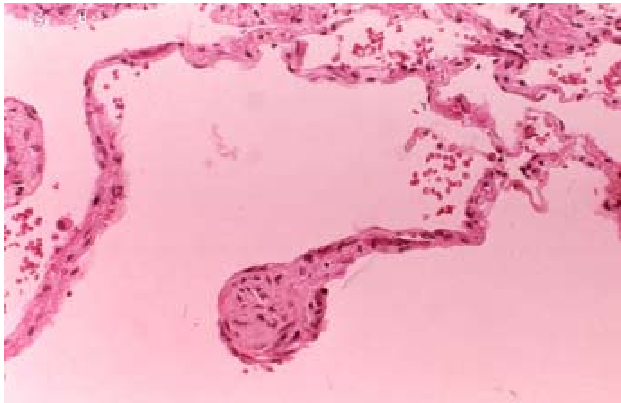
note that chronic bronchitis frequently coexists w/emphysema

Pathology

gross: hyperinflated

(ignore the squamous cancer in this picture)

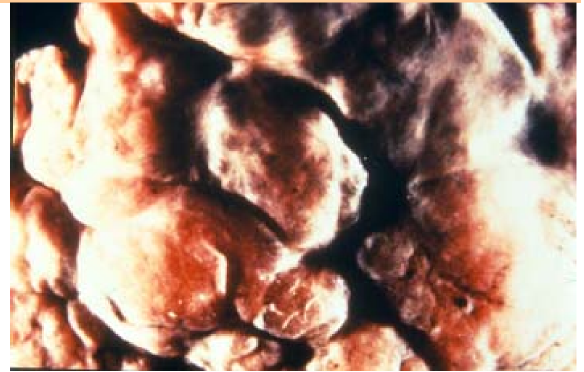
microscopically: enlargement of airspaces & loss of alveolar walls



Different types (defined by position in secondary lobule):

Centrilobular

- dilated airspaces in center of secondary lobule
- most common type of emphysema
- usually worse in upper lung
- looks like bunch of grapes from outside lung



Panlobular = Panacinar

- usually related to α-1-antitrypsin defect
- dilation and destruction involves entire secondary lobule
- much less common

Bullous

- not a true category, can occur w/ any type of emphysema
- a bulla is just a big cyst, nothing to get too excited about
- common, idiopathic

Clinical

CXR: bigger lung volume, low diaphragms. barrel-shaped thorax

Overview of Pleural Dz

What is the pleura?

- visceral: covers lung parenchyma
- parietal: covers endothoracic fascia
- blood supply: both systemic & from bronchial arteries
- lymphatics in parietal pleura: communicate w/pleural space through stomas
  - these stomas are the only exit for cells & liquid in pleural space
- mesothelium: flat squamous epithelium that makes up both pleural membranes

Pleural Effusion

Pathogenesis

- Normally (in health), you have a balance of starling forces that promote filtration of fluid INTO pleural space, but lymphatics drain this
  - Considerable (20x) ability of lymphatics to ↑ drainage
- But, there are several ways you can get too much fluid in the pleural space
  - ↑ P(capillary)
    - CHF
  - ↓ π(capillary)
    - nephrotic syndrome
  - ↑ permeability
    - leaky vessels, can be caused by pneumonia
  - ↓ lymphatic drainage of pleural space
    - tumor
    - fibrosis of lymphatic channels
  - movement of fluid from peritoneum
    - ascitis fluid through holes in diaphragm

Physiologic effects

- Restrictive ventilatory dysfunction
  - ↓ TLC
- diaphragm may be affected (disadvantageous part of length-tension curve)
- ABG: Δ's usually due to underlying lung dz, NOT pleural effusion
  - PaO2 usually ↓
  - ↑ A-a (V/Q mismatch)

Differential diagnosis

- Transudates
  - Criteria must include ALL the following, otherwise it's exudative
    - 1) pleural fluid to serum protein ration < 0.5
    - 2) pleural fluid to serum LDH ration < 0.6
    - 3) pleural fluid LDH that is < 2/3 upper limits of normal for serum LDH
  - Can be caused by relatively few things
    - CHF (most common)
    - Cirrhosis
    - nephrotic syndrome, etc
  - treatment is straightforward: treat underlying problem, diuresis
- Exudates: if exudate, "jump on it and get more tests": MANY diverse things can cause exudate. MUST figure out what!
  - infections
    - pneumonia most common
  - malignancy

Clinical

- Physical Exam
  - pleuritic chest pain
  - pleural friction rub w/inflammation
  - ↓ breath sounds
  - ↑ whispered pectoriloquy & egophony

Pleural Diseases:

Pneumothorax

Pathogenesis

- abnormal air in pleural space
- can have many causes, but regardless of cause, similar histology
  - spontaneous
    - rupture of subpleural bleb
  - underlying illness
    - bleb rupture, especially in CF
    - many infections
    - COPD
    - trauma
      - tension PTX: one way valve, ↑↑ pressure, trachia/mediastinum shift to OTHER side

Physiology

- decrease in vital capacity
- V/Q mismatch, ↓ PaO2, ↑ A-a

Pathology

- mesothelial proliferation in pleura = mesothelial hyperplasia
  - cells become cuboidal
  - may form little “polyps”, clump up
- fibrin deposition → fibrosis
- multinucleated giant cells

Clinical

- Physical exam
  - moderate tachycardia
  - ↓ breath sounds
  - hyperresonant percussion note
  - tactile femitus should be absent
  - w/tension PTX, trachea shifted towards other side

Pleural Plaques

Pathogenesis

- associated with asbestos
  - plaques are generally an indicator of asbestos exposure, but they do NOT signify asbestosis
- takes about 20 years to get a plaque after asbestos exposure
- pathogenesis poorly understood
- ↑ risk for mesothelioma

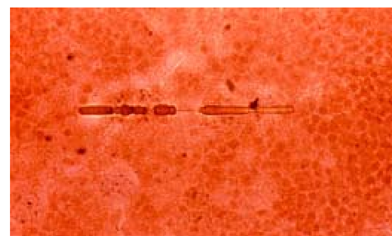
Pathology

- Gross
  - more on parietal and diaphragmatic pluera than visceral
  - parallel to ribs

  - may fuse and mimic mesothelioma

- Histology
  - basketweave collagen

  - very few cells, acellular
  - NO asbestos bodies (extremely rare to find one in a plaque)



  - may calcify

Pleural Diseases:

Mesothelioma

Pathogenesis

etiology unknown

strong association with asbestos

but we don't know for sure

takes 25+ years after exposure

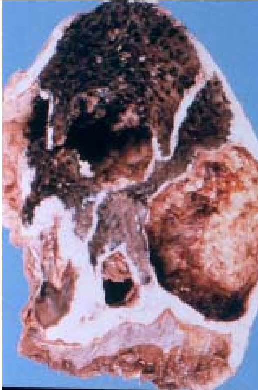
< 1% of all cancer deaths

Pathology

gross

more common on parietal pleura

White thick tumor that encases the lungs



NOTE: benign mesothelioma doesn't encase the lung

three types

1) Epithelial (50%): all have poor prognosis

solid

tubular

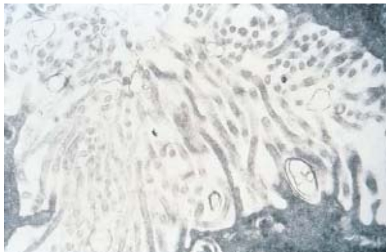
tubulo-papillary

2) Fibrous (25%)

3) Mixed (25%)

Can be vacuolated

have long and slender villi visible by EM



Pathophysiology

restricts lung from the outside

can also restrict pericardium

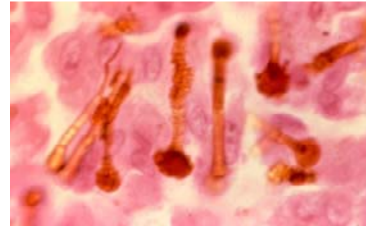
can spread to peritoneal cavity

Associated with asbestos

amphibole (crocidolite)

rod-like

when coated with glycoproteins & hemosiderin, called ferruginous body

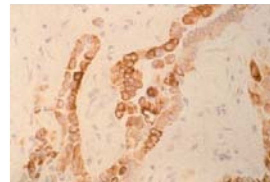


serpentine (chrysotile)

wavy

Diagnosis: special stain

+ cytokeratin & others



- CEA

Prognosis: poor

Pulmonary Thromboembolism & Pulmonary Infarcts:

Pulmonary Thromboembolism

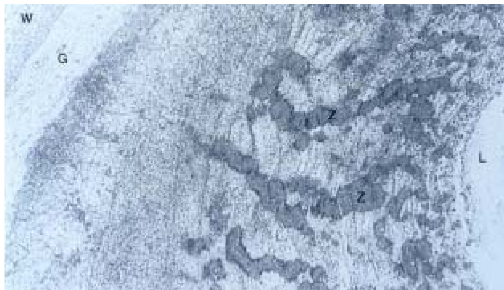
Pathogenesis

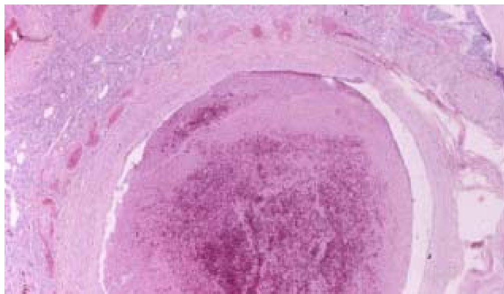
- may develop anywhere in venous system, especially pelvis & lower extremities
- risk factors
  - immobilization, CHF, fractures, estrogen, pregnancy, long rides
- four things can happen to a thrombus forming in the lower extremities:
  - 1) resorbed by fibrinolytic system
  - 2) incorporated into wall of vein
  - 3) break loose
    - if it forms in the calf it's probably too small to do any noticable damage
  - 4) grow larger and travel to deep venous system of thigh
    - this is where things can get dangerously big

Pathology

- premortem vs. postmortem clots
  - postmortem:
    - smooth tapering into adjacent branches
    - softer
  - premortem:

lines of zahn: platelets, fibrin, platelets, fibrin, etc





blunt-ended

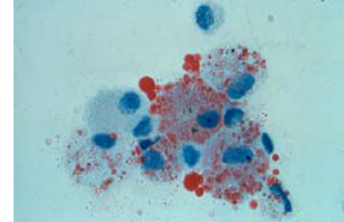
firmer

Pathological sequence

- thromboembolus may become incorporated into vascular wall
- later: intimal bands, web
- occasionally hypertensive vascular changes

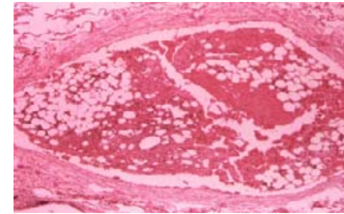
Other types of emboli

- Air emboli
  - frothy blood is main finding
  - differential dx: sepsis
- Fat emboli

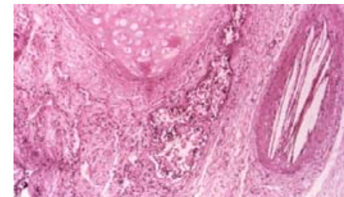


diagnosis: oil red "O" stain

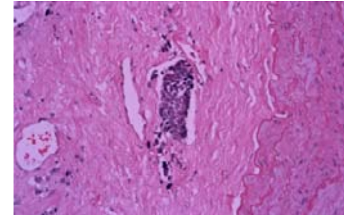
- Amniotic fluid emboli
- Marrow emboli



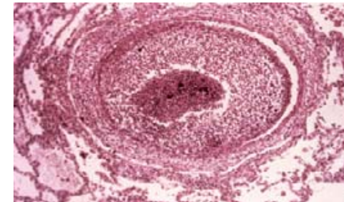
Cholesterol emboli



malignant emboli (small cell carcinoma)



septic emboli: clot is acutely inflamed



Pulmonary Thromboembolism (continued)

Clinical

- Detection
  - scintillation scan: look for lack of perfusion
- Acute presentations: cause of sudden death
  - +/- ↑ PA pressures
    - but does not always occur
  - +/- rapidly failing R heart
- ABG's
  - ↑ alveolar dead space: high V/Q ratio mismatch
  - ↓ $PaCO_2$ because minute ventilation ↑↑ out of proportion to ↑ in dead space
    - HYPERVENTILATION
    - anxiety, central drive to ↑ minute ventilation due to mediators
    - this can lead to alkalosis with an A-a gradient
  - hypoxemia may occur
  - ↑ A-a gradient due to 3 factors
    - 1) lower O_2 content in venous blood due to acute R heart failure and low CO
      - tissues suck more O_2 out of blood
    - 2) V/Q mismatch major cause of hypoxemia
      - ↑ deadspace
    - 3) there is an element of R → L shunt due to perfusion of unventilated areas
      - atelectasis can form due to loss of surfactant in involved lung region
- Can also present chronically: normal lung volumes, but ↓ DLCO
- Differential Dx/Patient presentation:
  - symptoms are NON-SPECIFIC to PE
    - dyspnea, fever, pleuritic chest pain, cough, hemoptysis, syncope, increased S2
  - Differential:
    - MI, COPD, pneumonia,
- CXR: not very helpful, can look normal or show many things
- It's important to figure out if it's really a PE because anticoagulation therapy is dangerous
  - impedence plethysmography
  - ultrasound
  - venous contrast
  - ventilation-perfusion lung scan (V/Q) scan
    - if normal, rules out PE
    - "high probably scan" + clinical suspicion = PE
    - "normal/low probablity scan" + clinical suspicion = 50% PE
  - pulmonary angiogram: invasive but gold standard
    - invasive, has risks
    - performed when someone could be at risk for anticoagulation (GI bleeds, etc)
  - D-Dimer test
    - only useful when negative

Treatment

- anticoagulation
  - course of treatment
    - heparin 7-10 days
    - coumadin 3-6 months
  - has risks
    - don't give heparin to someone with recent neurosurgery, for instance!
- venous filters
- fibrinolytic agents: these don't really work
- thrombectomy: last resort surgical option

Pulmonary Thromboembolism & Pulmonary Infarcts:

Pulmonary Infarcts

Pathogenesis

PE normally doesn't lead to infarct: lung has dual circulation

Risk factors:

- low-flow states
- ↑ Age

Pathology

Gross

- 75% of infarcts in lower lobes (this is where most of the blood flows)
- costophrenic angles: closest to ribs
- pyramidal/wedge shaped

Pathological sequence

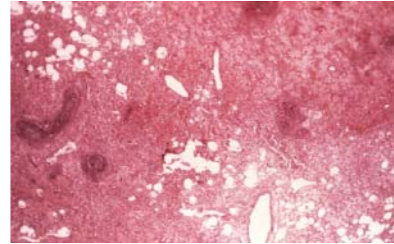
- initially: Red infarct due to edema & hemorrhage
- later: Pale infarct due to WBC's and macrophages
- complete necrosis may occur
- organization → scar

months to one year

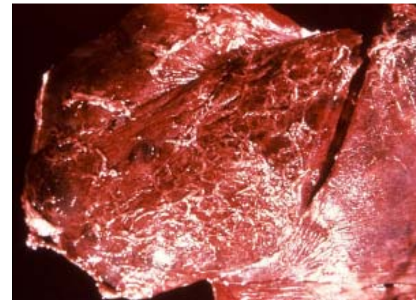
or, can get infected → abscess (2-3%)

this shows a fresh infarct @ 6 oclock and an infected one @ 3 oclock

Infected infarct



Can lead to breaks in pleural membrane → blood enters pleural space → fibrinous pleuritis



Clinical

Diagnosis:

CXR may be normal or show blurred shadow

Pulmonary Hypertension

Pathogenesis/Pathophysiology

- Normal physiology
  - Normal lung pulmonary artery pressure is about 25 mm Hg
  - Can ↑ to 30 mm Hg during exercise
    - ↑ blood flow through lung
  - in any case, it's around 1/5 to 1/6 of systolic pressure
- Etiologies: pulmonary HTN can develop from 4 mechanisms
  - 1) ↓ blood return to L ventricle
  - 2) ↑↑ Cardiac output
    - vascular bed unable to accommodate ↑↑ flow rates
  - 3) ↓ radius of pulmonary artery: Resistance related to radius to 4th power
    - vascoconstriction
    - occluded lumen
    - blood vessels squeezed from outside
  - 4) Idiopathic = essential = primary
- Another way to think about etiologies:
  - Hyperkinetic
    - intracardiac shunt: ASD, VSD
  - Passive
    - LV failure
    - mitral stenosis/obstruction
    - Left atrial obstruction: myxoma, thrombus
    - pulmonary venous obstruction
    - neoplasm
  - Obliterative
    - parenchymal dz
    - COPD (Obstructive dz)
      - bronchitis
      - emphysema: destruction of alveolar walls destroys vasculature → ↓ cross sectional area → ↑ resistance
      - bronchiectasis
    - Restrictive dz
      - parenchymal fibrosis
    - collagen vascular disease, vasculitis
  - Obstructive: obstruct pulmonary arteries
    - PE
    - other emboli
    - pulmonary schistosomiasis
  - Vasoconstrictive
    - hypoxemia & acidemia stimulates vasoconstriction
      - this is why home O2 supplementation is so important for COPDers
    - sleep apnea
  - Idiopathic
    - PPH: obliterative processof small vessels of unknown cause
      - poor prognosis
      - some respond to prostacyclin or Ca++ channel blockers
      - O2 can relieve vasoconstriction
      - NO good treatment short of heart-lung transplant
- Whatever the cause, once pulmonary HTN is sustained for some weeks, the changes are irreversible
  - smooth muscle hypertrophy
  - deposition of elastin
  - intimial proliferation
- Tends to get worse over time
- Note: pulmonary HTN not due to primary lung dz is called cor pulmonale

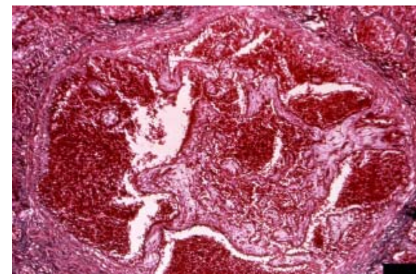
Pathology

SUMMARY OF HISTOPATHOLOGY IN PULMONARY HYPERTENSION

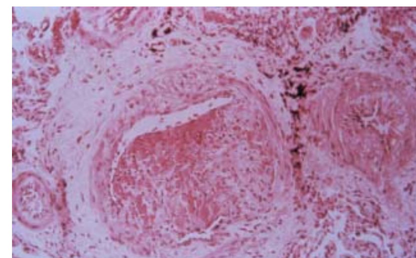
TYPE	SETTING	MH	IF	PPA
Obstructive	PTE	20%	Eccentric	No
Obliterative	ILD	Severe, near 100%	Concentric	No
Primary	? Drugs	No	No	Yes

MH = Medial Hypertrophy
IF = Intimal Fibrosis
PPA = Plexogenic Pulmonary Arteriopathy

- Obstructive = Occlusive HTN
  - usually thrombotic in nature, even if thrombi are not recognizable
    - PTE (pulmonary thromboembolism) usually does NOT give rise to sustained pulmonary HTN
    - It is only when a large proportion of arterial bed is occluded that pulmonary HTN develops
    - → probably a mechanical, NOT so much a vasoconstrictive effect
  - only 20% show medial hypertrophy
  - Clinically indistinguishable from PPA of primary HTN
  - Begins w/ thrombus: recanalization results in formation of intraarterial fibrous septa



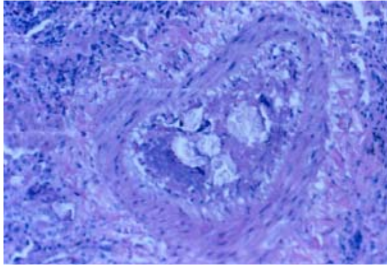
  - ends in eccentric intimal fibrosis or patches of cellular intimal proliferation



Pulmonary Hypertension:

Can also be caused by other types of thrombus:

- Talc thrombus (highly birefringent under polarized light) due to IV drugs

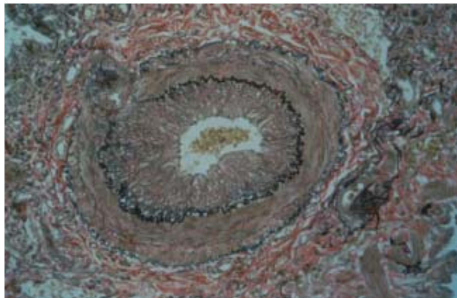


Obliterative = Fibrotic HTN

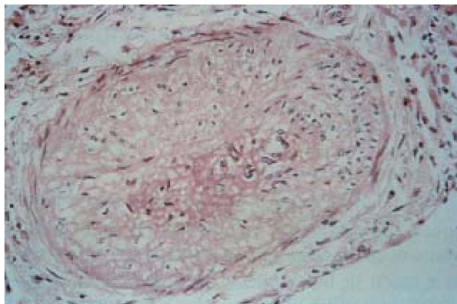
Usually due to interstitial lung fibrosis

- Clinically, pulmonary arterial pressure can actually be normal
- severe pulmonary HTN is uncommon w/ fibrotic disorders

Pulmonary arteries show severe medial hypertrophy and concentric intimal fibrosis



both media & intima involved: here there is so much intimal proliferation there no lumen is left

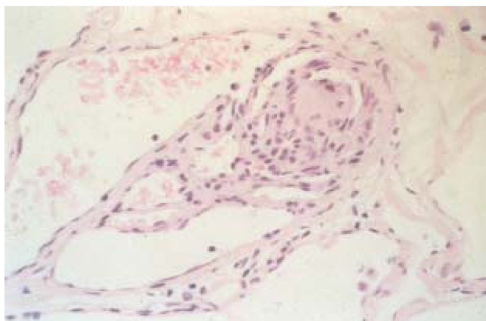


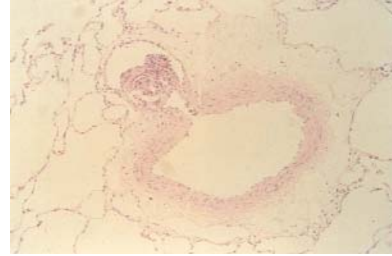
both arteries & veins can be affected

Idiopathic = PPH (primary pulmonary HTN)

Not associated with PTE or ILD

Plexogenic Pulmonary Arteriopathy (PPA) is hallmark, but not pathognomonic: capillary tufts





PPA classified by Heath-Edwards Classification

A bunch of disclaimers about PPH

- Pathogenesis is a big stinking question mark
- No treatment
- Histopatology is not specific
  - May overlap with other disorders

Clinical

ABG's

- hypoxemia due to altered V/Q relationships & shunts through regions not normally perfused

Symptoms

- poor exercise tolerance and severe dyspnea on exertion
- some patients: dull substernal chest pain

Physical Exam

- loud P2
- narrowly split S2
- signs or RV heart failure

CXR: enlarged hilar shadows

- could show RA or RV enlargement

Tests

- pulmonary HTN detected w/ dopper echocariographic studies
- confirmed w/ right heart cath

Respiratory Control

Chemoreceptors

- medullary:
  - detect ↑ $PaCO_2$ and/or acidosis to increase breathing rate
  - detect ↓ $PaCO_2$ to decrease breathing rate
    - decreased breathing rate may also result from ↓ sensitivity
      - athletic training
      - aging
- carotid body: detect ↓ PaO_2
  - normally, hypoxia above 70 mm Hg does not stimulate breathing
  - but once hypoxia gets below 70, ventilation will ↑↑
- Resting minute ventilation determined primarily by $PaCO_2$
  - But, combine hypercapnia (principle trigger) with hypoxia (secondary trigger) to produce an even greater response in minute ventilation than either response alone

Mechanoreceptors: 3 types

- 1) strech receptors in smooth muscle of airways
  - inhibit inspiration as lung is inflated
- 2) irritant-receptors in airway epithelium
  - cough in response to noxious agents
- 3) juxtacapillary receptors in lung interstitum
  - the only unmyelinated fibers
  - stimulated by interstitial edema & chemical agents
  - stimulation causes laryngeal closure & rapid shallow breathing

Rhythmogenesis & Sleep

- Physiologic Δ's
  - hypoventilation is normal (↑ $PaCO_2$, ↓ PaO_2)
  - ventilatory set point altered
  - respirations can become irregular
  - chemoreceptor response blunted
  - floppy airway
  - → these Δ's are not a big deal in healthy people. But w/ underlying lung dz they can be huge problem.
    - It is not unusual for COPDer to have ↓35% decline in PaO_2 during sleep
- obstructive sleep apnea (OSA)
  - Apnea: absence of airflow and tital volume for ≥10 secs
  - Hypopnea: ↓ in tidal volume by >25% for ≥ 10 secs
  - OSA: upper airway obstruction in pharynx (can be reversed with tracheostomy)
    - near closure of airway → snoring
    - complete closure of airway → OSA
  - Systolic BP ↑↑ due to inspiratory efforts against closed airway
  - these cyclic alterations in pulmonary arterial pressures may lead to daytime pulmonary HTN (seen in 20-60% of OSA patients)

Respiratory Failure

Definition arbitrary: any disorder that results in "abnormally" ↓ PaO_2 (< 60 mm Hg) with/without "abnormally" ↑ $PaCO_2$ (> 50 mm Hg)

Hypoxemic vs. Hypercapnic failure

- "Lung Failure"
  - first hypoxemia then hypercapnea
  - @ first hypoxemia, then if you get bad enough → hypercapnea
- "Pump Failure" = outside lung dz
  - ALWAYS hypercapnea due to ↓ minute ventilation
  - ↓ PaO_2
  - ↑ PCO_2
  - NORMAL A-a gradient
- Or, you could have BOTH
  - Healthy people have a considerable reserve to ↑ minute ventilation, but people with underlying lung dz are extremely sensitive to extra insults

Pathophysiology

- Volume of CO_2 eliminated related to:
  - 1) concentration of CO_2 in alveolar gas: can be ↑ in many ways
    - a) hyperthermia, shivering
    - b) ↑ work of breathing increases CO_2 metabolism in respiratory muscles
    - c) not enough ventilation
  - 2) alveolar ventilation: in "pump" failure, tidal volume is reduced → ↑ dead-space
    - a) CNS depression (drugs)
    - b) mechanical defects (flail chest, extreme hyperinflation)
    - c) fatigue of respiratory muscles
    - → only CNS depression doesn't ↑ work of breathing

Clinical Correlations: How different diseases can cause respiratory failure

- Pump failure
  - CNS depression
  - PNS diseases
  - Chest wall diseases
  - Upper airway obstructions
- Lung diseases: asthma, COPD, CF, pneumona, ARDS
  - combined mechanisms of severely limited ventilatory supply & ↑↑ ventilatory demand
  - profound hypoxemia can result due to significant V/Q mismatch +/- R → L shunts
  - Early: respiratory alkalosis as long as ventilatory supply > demand
  - Late: respiratory acidosis as patient gets too tired to breath or cannot breath enough: ventilatory supply < demand

Treatment

- too many nuances for now
- In general, treat primary problem regardless of respiratory failure
- Correct hypoxemia/hypercapnia without causing additional complications such as O_2 toxicity or barotrauma
- don't worry about it (yet)

Pulmonary Infections

Pathogenesis

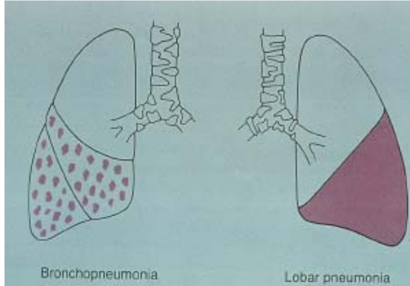
URT infections: most often viruses

true pulmonary infections: viruses, mycoplasma, bacterial, mycobacterial, fungal

Bacterial Pneumonia

General

Two types: Lobar vs Lobular (Bronchopneumonia)



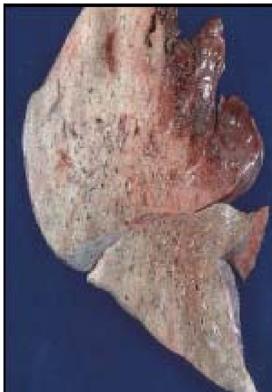
lobar starts in alveoli and spreads through pores of Kohn

lobular (bronchopneumonia) starts in terminal and respiratory bronchioles and spreads through bronchial walls into alveoli

Definition: lower respiratory tract infection by bacteria

Most common cause: Streptococcus pneumoniae (pneumococcus)

can be very aggressive and result in tissue necrosis (note necrosis & hemorrhage @ 12 oclock)



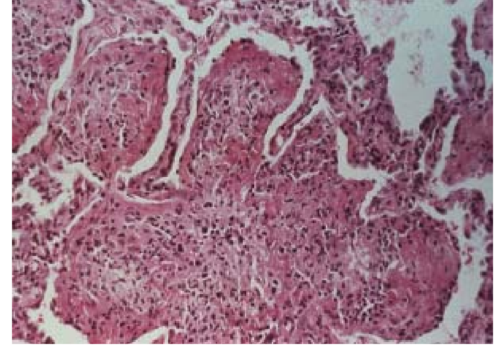
Lobar pneumonia: starts in alveoli, spreads through pores of Kohn

95% caused by pneumococcus

also klebsiella, pseudomonas, etc

Widespread fibrinosupurative consolidation of large areas (and even whole lobes) of lung

Extensive exudation through pores of Kohn (little openings between alveoli)



Four stages (mostly historical) of Lobar Pneumonia:

1) Congestion

heavy and red lungs

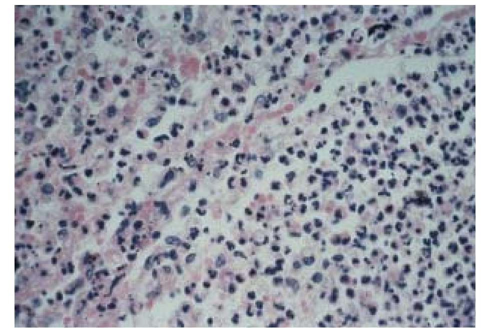
vascular engorgement

few polys, many bacteria

2) Red Hepatization: liver-like

red, firm, airless

MANY polys, fibrin, RBCs

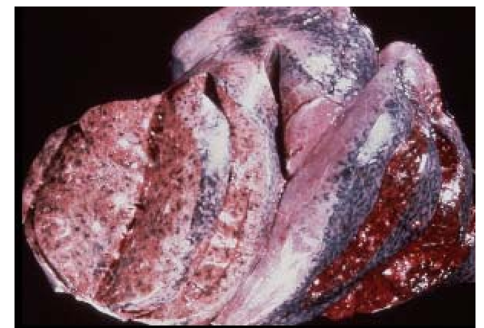


3) Gray Hepatization

gray brown dry surface

disintegrated RBCs, fibrino-purulent exudate

gray (left) and red (right)



4) Resolution

enzymatic digestion

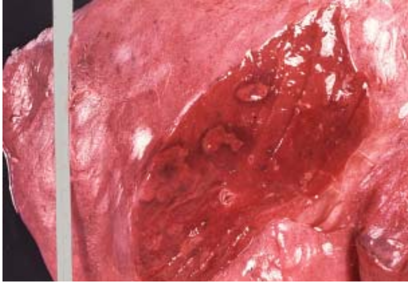
granular depris

pleural fibrain exudates

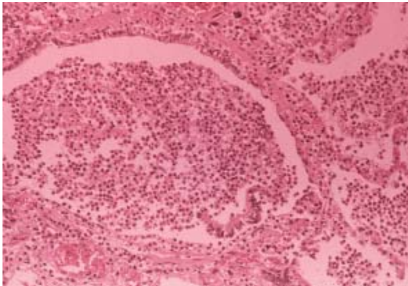
Pulmonary Infections

Lobular = Bronchopneumonia: starts in airways

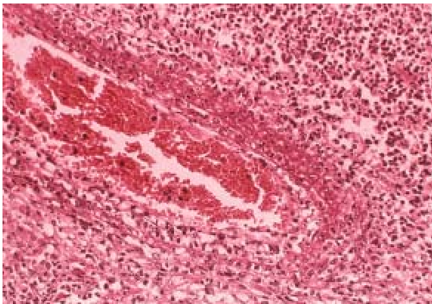
starts in terminal and respiratory bronchioles and spreads through bronchial walls into alveoli



airway filled with PMNs: acute inflammation of airways



blood vessels can get inflamed

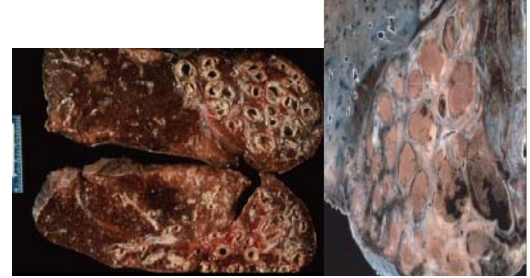


caused by many pathogens:

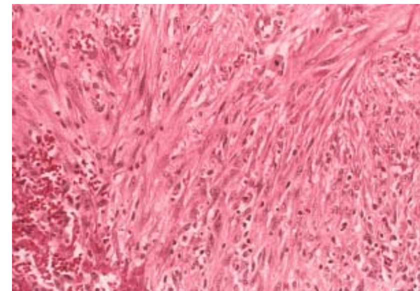
streptococci, pneumococci, staphylococci, H. flu, P. aeruginosa

Complications of Bacterial Pneumonia

1) Bronchiectasis: abnormal dilation of airways, can only be cured w/surgery



2) Spread to pleura → empyena: fibroblasts, RBCs, neutrophils affect pleura (needs surgical management)



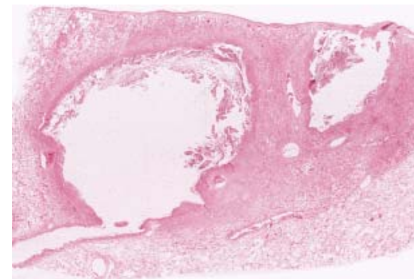
3) Necrosis → abscess: see below

4) organizsation → solidification

5) bacteremia → seeding

Bacterial Lung Abcess

Definition: local suppurative process characterized by necrosis



Pathogenesis

1) **aspiration** (most common)

2) antecedent bacerial infection/pneumonia

3) septic emboli

4) neoplasia: becomes necrotic & infected w/ bacteria

Types of bacteria

bacteroides, fusobacterium, peptococcus

VERY foul breath

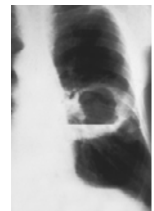
Pathology

cardinal sign: necrosis

more common on R side

fibrosis w/chronic cases

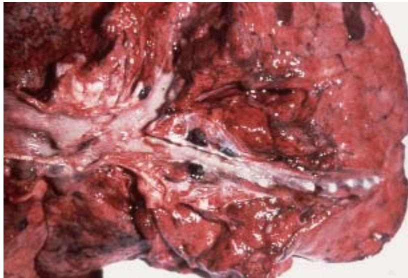
fluid line on x-ray



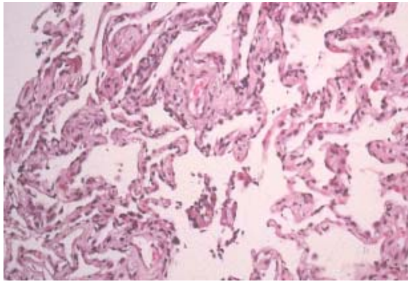
Pulmonary Infections

Atypical Pneumonia: confined to interstitium

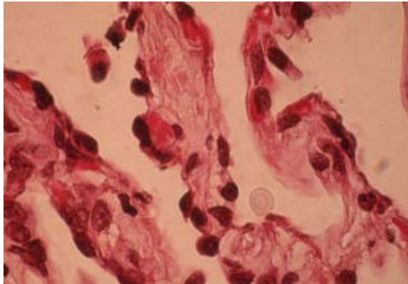
- Lack of alveolar exudates
- the world would be a better place if it was called "interstitial pneumonia"
- primarily caused by Mycoplasma or viruses
- Pathology of atypical pneumonia
  - Gross:
    - not too much to see except congestion



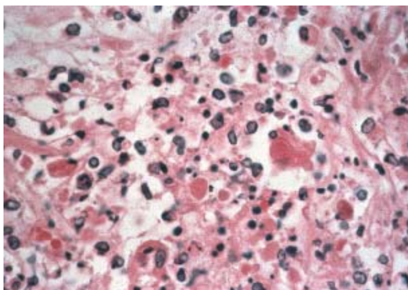
  - Histologically:
    - expansion of interstitum, NO exudate



Cells lining alveoli are hyperchromic. No PMN's

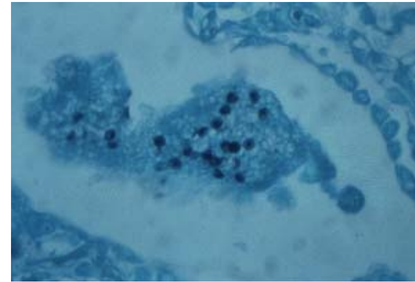


Viral atypical pneumonias are similar to mycoplasma pneumonia but tends to be necrotic, and you can see viral inclusions



PCP pneumonia

- AIDS, AIDS, AIDS
- causes frothy exudate



Lung Cancer

Pathogenesis

Early changes: these changes are probably reversible

squamous metaplasia

repiratory epithelium responds to chronic damage by changing from pseudostratified ciliated columnar epithelium to stratified squamous

dysplasia

considered pre-malignant

Carcinoma in situ

becomes carcinoma once cells cross basement membrane

Carcinoma

progression from mild dysplasia to carcinoma takes about 15-20 years

add another 10 years for cancer to be detectable by CXR

now it's too late to be cured by surgery alone

Paraneoplastic syndromes: findings in cancer patients which canot be explained on the basis of spread of tumor: often ectopic hormone production

ectopic hormone production

↑ ACTH: cushings

↑ 5HT: carcinoid syndrome

↑ ADH: SIADH

↑ PTH: Hypercalcemia

↑ Gonadotropin: gynecomastia

↑ TSH: hyperthyroidism

Neuromuscular syndromes

dermatomyositis-polymyositis

MG

Unknown cause

hyeprtrophic pulmonary osteoarthropathy

Etiology

85% due to cigarette smoking

asbestos, radon, radiation, chemicals also play a role

Classification schemes

WHO

1) Squamous cell carcinoma

2) Adenocarcinoma

3) Large cell carcinoma

4) Small cell carcinoma

Working classification

Non Small Cell

squamous cell

adenocarcinoma

large cell

Small cell

classic

mixed (small and large cell)

Combined

Pathology

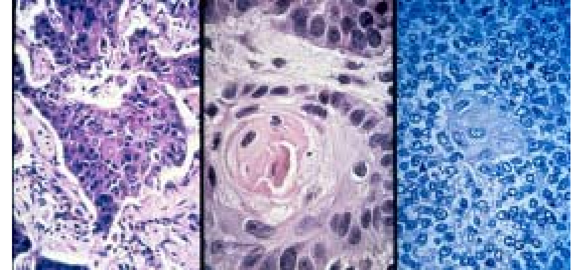
Squamous Cell Carcinoma

80% male

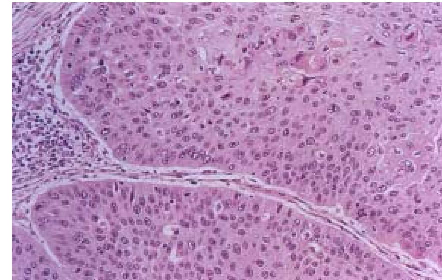
most closely associated with cigarette smoking

may present w/obstructive pneumonitis

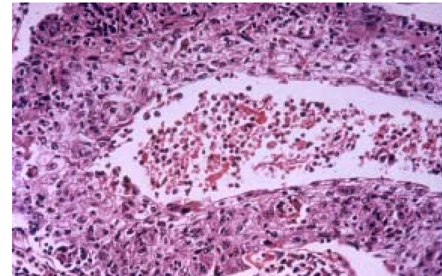
charactarized by presence of keratin to form pearls (keratin can be intracellular or extracellular)



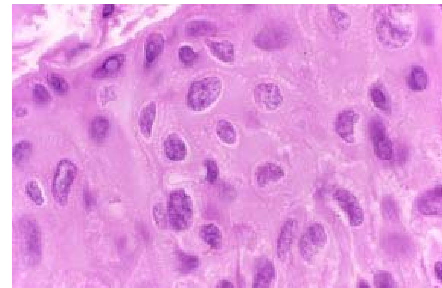
squamous cell carcinoma



Has a tendancy to undergo necrosis & cavitate



can have intracellular bridges: spines which connect one cell to the next, looks like railroad tracks



gross: central tumors which cavitate

Lung Cancer:

Pancoast tumor

- a tumor that that grows in the superior sulcus of lung
- most often (95%) NSCC, but can be squamous or adenocarcinoma
- often screws w/ brachial plexus or sympathetics → horners

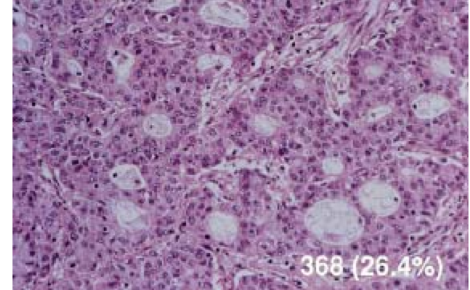
Adenocarcinoma

- 50% of lung cancer in women
- M = F, ↑ prevalence in women
- Cavitation is unusual (in contrast to Squamous)
- forms tubules and glands. Can form papillary structure
- 77% involve pleura, often comes very close to pleura

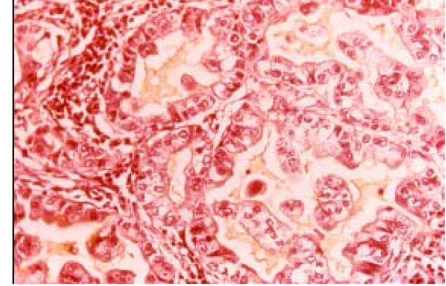
- may simulate mesothelioma

Four Types of Adenocarcinoma

1) Acinar: forms glands



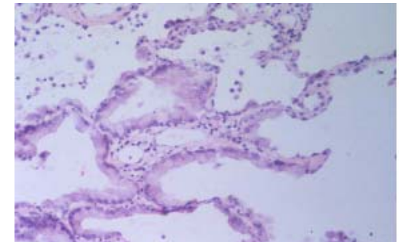
2) Papillary



3) Solid

4) Bronchoalveolar

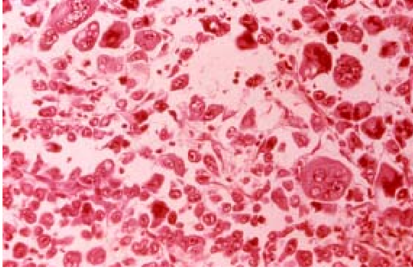
- NOT associated with smoking
- can look like metastatic cancer to lung (ovary, pancreas, breast, stomach)
- mucin producing cells
- follows preexisting alveolar framework



Lung Cancer:

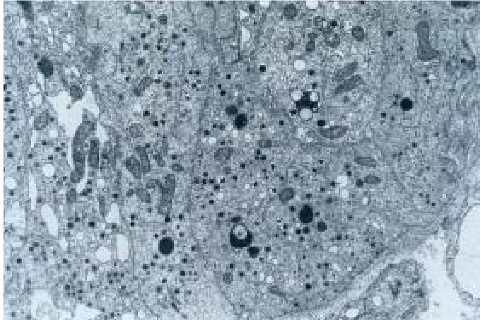
Large Cell Carcinoma

- too poorly differentiated to have squamous or glandular (adeno) features, so it's just called "Large Cell"
- In the real world, they are simply called "Non Small Cell Carcinomas"
- very aggressive, poor prognosis

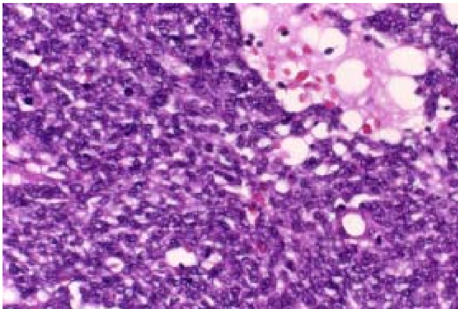


Small Cell Carcinoma

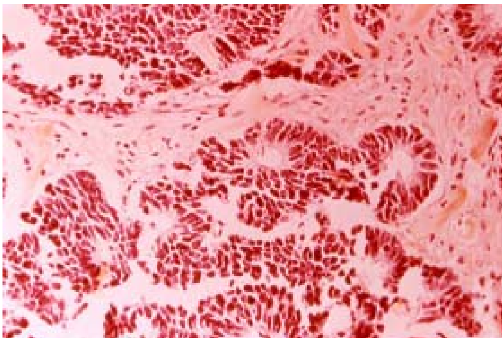
- derived from neuroendocrine cells
  - commonly can have ectopic hormone production: paraneoplastic syndromes
  - neurosecratory granules visible by EM



- Responsive to chemotherapy/Radiation
- Small cells w/ little cytoplasm



- Can form Rosettes: evidence of neuroendocrine differentiation



Occupational Lung Diseases

Pneumoconiosis: "dusty lungs": fibrotic rxn of lung that results from inhalation of inorganic dusts

Asbestosis

General Description

- slowly progressive diffuse pulmonary fibrotic dz caused by inhalation of asbestos fibers
- Pleural involvement is hallmark (unique to asbestosis)
- Asbestos can also cause:
  - focal/diffuse pleural plaques
  - malignancies (bronchogenic and malignant mesothelioma)
  - pleural effusions
- Asbestos comes in two shapes:
  - long curly strands (serpentine)
  - long straight rods (amphibole)

Disease course

- 20-30 year lag time after exposure (larger exposure → shorter lag)

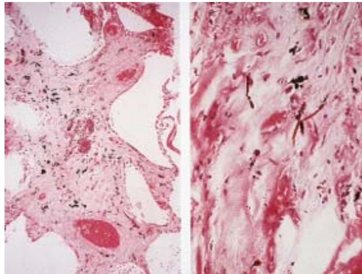
PFTs: restriction w/ ↓ DLCO and ↓ exercise tolerance (oximetry)

CXR: bilateral interstitial reticular (fine lacey) or multinodular abnormalities

- especially in lower lung
- often with associate pleural sbnormalities
- Hilar mediastinal adenopathy usually NOT seen

Diagnosis:

- presence of asbestos bodies in lung tissue associated with IPF (= UIP)



Therapy:

- no specific therapy.

Complications:

- respiratory failure & malignancy
- asbestos is the only known risk factor for malignant mesothelioma

Silicosis

General Description

- chronic dz caused by inhalation of dusts containing free crystalline silicon dioxide
- results in multiple nodular parenchymal and lymphoid lesions
- fibrotic lesions of pleura
- ↑ risk of lung cancer
- ↑ risk of TB

chronic and accelerated/acute forms

- chronic: requires long exposure
- acute & accelerated: high concentration quartz exposures as short as a few weeks (acute) to 5 years (accelerated)

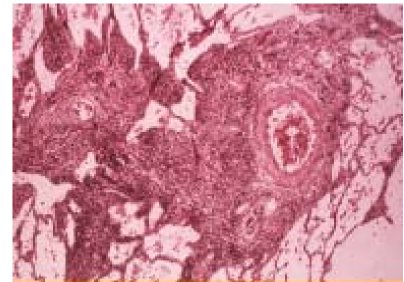
pathogenesis:

- silica is fibrogenic substance
- → macrophages eat it and then they die
- → lysis of macrophages release fibrogenic cytokines
  - IL-1
  - TNF
  - Fibronectin

Pathology

- Gross: scarring has contracted the upper lobe into small dark mass

- Microscopically: perivascular nodules



Pathophysiology: Silicosis causes two things

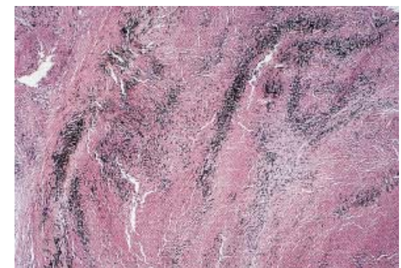
- 1) narrowing/distortion of bronchial lumen by nodules → obstruction
- 2) hypertrophy/scarring of lymphoid tissues causes airway compression → mix of obstructive & restrictive

Treatment: primary prevention

Coal Worker's Pneumoconiosis

General

- What the hell? Do people even use coal for anything? Why don't we learn about papyrus lickers disease or lamb sacrifice lung or bronzesmithing bronchitis?
- primary lesion: coal macule
- Caplan's syndrome:
  - association between CWP and rheumatoid arthritis



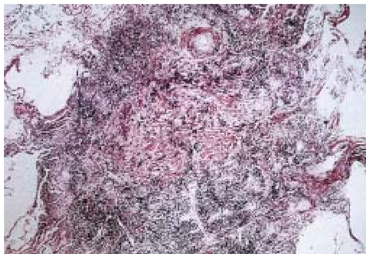
- ↑ risk of TB, not not as high an increase as w/silicosis

Occupational Disease:

Coal can cause 3 diseases:

1) anthracosis
   - virtually asymptomatic, no tissue response
2) Simple CWP
   - coal dust accumulates in lung with no dysfunction
   - Coal Macule: centrilobular coal deposit made of macrophages and coal dust. No collagen

   - Coal Nodule: centrilobular dust nodule w/ macrophages & collagenization



3) Progressive massive fibrosis (PMF) with extensive fibrosis

Clinical Course
- usually benign
- can cause pulmonary HTN, cor pulmonale
- no known ↑ in risk for cancer

Occupational Asthma/RADS

Occupational Asthma

General
- variable airflow limitation and airway hyperresponsiveness caused by a particular occupational encironment
- NOT due to stimuli encountered outside of workplace
- occurs in 5% of subjects exposed to proteinaceous high molecular weight agents and in 5-10% exposed to low molecular weight chemical agents
- Most common cause: isocyanates (used for production of plastics and rubber)
- Risk of developing OA is a function of intensity of exposure
- After individual is sensitized, ANY FUTURE EXPOSURE CAN KILL THEM (bronchospasm)

Clinical
- similar to nonoccupational asthma
- Patient has symptoms at work or within several of finishing work, but decline of symptoms when not at work
- Positive methecholine challenge

Treatment
- Must remove patient from further exposures
- drug therapy is same as for normal asthma, but CANNOT serve as substitute for changing jobs

RADS

General
- persistent (> 3 months) asthma-like illness after a SINGLE exposure to an irritant
  - an OBVIOUS bad thing happened to them
  - i.e. a tanker poured gas all over them

Clinical
- Negative methecholine test: symptoms NOT reproducable
- most people will have complete resolution, but some will end up with persistent asthma-like symptoms
- RADS airway obstruction LESS responsive to bronchodilators than asthma obstruction is

Hard Metal Diseases

Rare disease related to rare compounds (involving military or aerospace)
- cobalt is the toxin

Disease
- can resemble interstitial lung disease
  - giant cell interstitial pneumonitis-like histopathology
- can also look like HSP or occupational asthma

Occupational: General Clinical Notes

Presentation
- No specific clinical features, but certain diagnostic features help
- Clubbing: Asbestosis only
- End-inspiratory crackles: Asbestosis (pulmonary fibrosis) or HSP

CXR:
- ↑ interstitial markings
  - asbestosis
  - HSP
- nodular densities
  - silicosis
  - coal worker’s pneumoconiosis
- “eggshell” calcifications of hilar lymph nodes
  - silicosis
- pleural placques/effusions
  - asbestosis

PFTs
- can be obstructive, restrictive, or mixed

Biopsy not required clinically (but it may be legally)