Primary Cast Episode 25 - Respiratory Pathology

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1. **ARDS**

Describe the pathogenesis of ARDS

- Injury to alveolar capillary membrane
- Acute inflammatory response (neutrophil mediated)
- Increased vascular permeability - leads to alveolar flooding
- fibrin deposition
- Formation of hyaline membranes
- Widespread surfactant abnormalities (damage to type II pneumocytes)
- Eventually leads to organisation with scarring

What conditions are associated with the development of ARDS?

- Infection - sepsis, diffuse pulmonary infection, gastric aspiration
- Physical/injury - trauma to head, near drowning, burns or radiation
- Inhaled irritants - O2 toxicity, smoke, irritant gases and chemicals
- Chemical injury - barbiturates, heroin, paraquat
- Haematological conditions - multiple transfusions, DIC
- Other - pancreatitis, uraemia, cardiopulmonary bypass

2. **Asthma**

What is the definition of asthma?

Asthma is a chronic disorder of the conducting airways, usually caused by an immunological reaction, which is marked by episodic bronchoconstriction due to increased airway sensitivity to a variety of stimuli, inflammation of the bronchial walls and increased mucus secretion

Describe the pathogenesis of acute atopic asthma

- It is a classic example of IgE mediated (Type 1) hypersensitivity
- Atopic triggers include: environmental allergens e.g. dust, pollen, dander, food
- On re-exposure to the antigen, the antigen induces cross linking of IgE bound to previously sensitised mast cells .
- These mast cells release preformed mediators that directly and indirectly via neuronal reflexes result in bronchospasm, increased vascular permeability, mucus production and recruitment of leukocytes

What are potential triggers for non-atopic asthma?

- Respiratory viruses, air pollutants, exercise, cold
- Can also be drug induced i.e. aspirin
- Occupational triggers - fumes from epoxy or resins, organic and chemical dusts (wood, cotton), gases or other chemicals (formaldehyde/penicillin)
- Cigarette smoke also a trigger

3. **Bronchiectasis**

What is bronchiectasis?

A disease characterised by permanent dilation of bronchi and bronchioles caused by destruction of the muscle and elastic tissue, resulting from or associated with chronic necrotizing infections. Also involves scarring and persistent infections.

What conditions are associated with the development of bronchiectasis?

- Congenital/hereditary conditions - cystic fibrosis, immunodeficiency, ciliary dyskinesia
- Post infectious - usually necrotising pneumonia - staph aureus, haemophilus, TB, pseudomonas, some viral and fungal infections
- Bronchial obstruction - tumour or foreign body, mucous impaction
- Idiopathic in 25-50% of cases

4. **Fat Embolism**

What clinical conditions can cause a fat embolism?

- Anything that results in fat globules travelling within the circulation
- Most commonly long bone fractures - common in severe trauma but <10% are clinically significant
- Can rarely occur with burns and soft tissue trauma

What is the pathogenesis of fat embolism syndrome?

- Mechanical obstruction of microvasculature in the lungs and brain by fat globules, aggregated platelets and RBCs
- Biochemical injury from FFAs from fat globules causing endothelial injury, platelet activation and mediator release

What are the potential clinical sequelae of fat embolism?

- Majority are asymptomatic
- Neurological - altered LOC
- Pulmonary - tachypnoea, dyspnoea, hypoxia
- Haematological - thrombocytopaenia and anaemia

5. **Pulmonary Embolism**

Describe the pathogenesis of thrombotic pulmonary embolism

PEs originate from deep vein thrombosis (the majority from the lower limb)
Fragmented thrombi from DVTs are carried through the venous system and into the right side of the heart before lodging in the pulmonary arterial vasculature including the main pulmonary artery, the artery bifurcation or the smaller branching arteries

What factors determine the severity of the pathophysiological response to a pulmonary embolism?

- Extent of pulmonary artery blood flow obstructed (Main one and the answer needed to pass)
- Size of the vessel occluded
- Number of emboli
- Overall cardiovascular status
- Release of vasoactive factors, such as thromboxane A2

What are the symptoms and signs of a pulmonary embolism?

Clinical manifestations depend on the size and location of the thrombus in the pulmonary vasculature

Most PEs are small and produce no symptoms or signs at all (estimated 60-80% are asymptomatic)

Symptoms

- Chest pain - typically pleuritic
- Dyspnoea
- Syncope

Signs

- Hypoxia
- Tahypnpoea
- Tachycardia
- Hypotension
- Shock/sudden death
- Acute right heart failure
- Fever
- Haemoptysis

What are some risk factors for PE?

Primary factors - factor V leiden, antiphospholipid syndrome, prothrombin mutations

Secondary factors - obesity, OCP, cancer, immobilisation, long haul flights, pregnancy, central venous line, hip fractures

What are the potential clinical sequelae of a pulmonary thrombo-embolism?

Again, this relates to the size and number of emboli and overall state of the underlying cardiovascular status.

- Majority are asymptomatic
- Severe PEs can cause sudden death
- Large PEs can cause haemodynamic compromise and shock
- PE can lead to pulmonary infarction causing some of the signs and symptoms listed above
- May also cause pulmonary hypertension

List 2 other types of emboli

- Fat embolism
- Air embolism
- Amniotic fluid embolism
- Foreign body i.e. fragment of a catheter
- Tumour embolism

6. Emphysema

What is emphysema?

A chronic lung condition characterised by irreversible enlargement the airspaces distal to the terminal bronchiole, accompanied by destruction of alveolar walls without fibrosis

Describe the pathogenesis of emphysema

- Loss of cellular homeostasis - caused by exposure to toxic substances such as tobacco smoke and inhaled pollutants which induces ongoing inflammation, epithelial cell death and extracellular matrix proteolysis
- Protease-antiprotease imbalance leading to destructive protease activity
- Alpha 1 antitrypsin is a major protease inhibitor and a hereditary deficiency can lead to emphysema at a younger age
- Accumulation of neutrophils, macrophages and lymphocytes results in the release of elastases, cytokines and oxidants that cause epithelial injury and proteolysis of the extracellular matrix
- Elastin degradation products further increase the inflammation
- Smoke depletes antioxidant mechanisms, further adding to the damage
- The end result is destruction of the alveolar walls without fibrosis

What are the anatomical types of emphysema?

- Centriacinar - involves the central or proximal parts of the respiratory unit - the acinus - sparing the distal alveoli. Involves the upper lobes and apices, primarily occurs in male smokers associated with chronic bronchitis *(MOST COMMON - 95%)*
- Panacinar - uniform - alpha-1-antitrypsin deficiency . Pattern of destruction is chronic low level destruction. Lower basal zones, uniform destruction.
- Distal acinar or paraseptal - causes spontaneous pneumathoraces
- Irregular - airspace enlargement
- Bulous - blebs
- Interstitial emphysema
- Compensatory - following lobectomy
- Obstructive overinflation - from a partial blockage

What are the possible complications of emphysema?

- Bullous lung disease
- Expiratory airflow limitation
- Infection
- Respiratory failure
- Pneumothorax
- Cor pulmonale and congestive heart failure

What is the role of cigarette smoke?

- Smokers have higher numbers of macrophages and neutrophils in the alveoli because smoking stimulates neutrophil chemotactic factors and also activates the alternative complement pathway
- Smoking stimulates release of neutrophil elastase, proteinases
- Smoking increases elastase activity in macrophages
- ROS in smoke deplete glutathione and superoxide dismutase

How do the clinical features of emphysema differ to those with chronic bronchitis?

This is referring to the syndromes of pink puffer (emphysema) vs blue bloater (chronic bronchitis)

The pink puffer syndrome phenotype is barrel chested, dyspnoeic, prolonged expiration, hyperventilation. Relatively normal gas exchange until late stage in the disease process.

Blue bloater describes a phenotype of recurrent chest infections with purulent sputum, less dyspnoea, decreased respiratory drive. Patient is typically hypoxic and cyanotic. Peripheral oedema results from cor pulmonale and RV failure.

7. Lung Cancer

What factors predispose to lung cancer?

- Tobacco smoking is the key factor - associated with daily amount and duration of habit
- Environmental exposures - radiation, asbestos, air pollution (particulates), occupational inhaled substances (nickel, chromates, arsenic)
- Genetic mechanisms - dominant oncogenes (c-MYC, k-RAS) & loss of tumour suppressor genes (p53, RB)
- Precursor lesions - squamous dysplasia, carcinoma in situ, atypical adenomatous hyperplasia

What are the classical clinical features of lung carcinoma?

- Cough
- Weight loss
- Chest pain
- Dyspnoea

What are the main categories of primary lung cancer?

Adenocarcinoma - more common in women

- Squamous cell carcinoma - more common in men
- Small cell carcinoma - very malignant
- Large cell carcinoma

What are the pathways by which a malignant tumour might spread?

- Local invasion
- Direct seeding of cavities/surfaces
- Lymphatic spread
- Haematogenous
- Surgical instruments
- Nerves

What are the clinical effects of local spread of lung tumour?

- Airway obstruction = pneumonia, abscess, lobar collapse
- Obstruction of the SVC leading to SVC syndrome
- Pleural effusion
- Pericarditis or tamponade
- Hoarseness (from involvement of the laryngeal nerve)
- Dysphagia (from oesophageal obstruction)
- Pain from rib destruction
- Diaphragmatic paralysis (due to phrenic nerve involvement)
- Horner syndrome (from sympathetic ganglia)

What paraneoplastic syndromes are associated with lung carcinoma?

Paraneoplastic syndromes are clinically significant in less that 10% of patients

- SIADH - hyponatraemia (predominantly small cell)
- ACTH excess - cushing's syndrome (predominantly small cell)
- Parathyroid hormone/PTH-related peptide - hypercalcaemia (predominantly small cell/squamous)
- Calcitonin - Hypocalcaemia
- Gonadotropins - gynaecomastia
- Serotonin/bradykinin - carcinoid syndrome

Describe the relationship between asbestos exposure and malignant mesothelioma

- There is an increased incidence of malignant mesothelioma among people with heavy exposure to asbestos. The lifetime risk is approximately 7-10%
- Asbestos bodies are found in increased numbers in the lungs of patients with mesothelioma
- There is a long latent period for mesothelioma of approximately 25-45 years

- There is no increased risk in asbestos workers who smoke (in contrast to asbestos related lung carcinoma)
- Asbestos workers are more at risk of dying from lung carcinoma than mesothelioma, especially if they smoke

Where can malignant mesothelioma arise?

- Pleura
- Peritoneum
- Pericardium
- Tunica vaginalis
- Genital tract

8. Community Acquired Pneumonia

What are the most common causes of community acquired pneumonia?

- Strep pneumoniae
- Mycoplasma pneumoniae
- Haemophilus influenzae
- Moraxella catarrhalis
- Staph aureus
- Klebsiella pneumoniae
- Pseudomonas aeruginosa
- Legionella pneumoniae

(Note: Pass is strep pneumoniae plus any 2 others - 2017)

What factors predispose patients to the development of acute bacterial pneumonia?

- Extremes of age
- Underlying chronic disease such as COPD, diabetes, cardiac failure, malnutrition
- Immunodeficiency from abnormal splenic function or asplenia

What are the pathological patterns of bacterial pneumonia?

- Bronchopneumonia: patchy consolidation of the lung, areas of acute suppurative inflammation, may be patchy through one lobe but is more often multilobar and frequently bilateral and basal because of the tendency of secretions to gravitate into the lower lobes
- Lobar pneumonia: fibrinosuppurative consolidation of a large portion of a lobe or an entire lobe. Patterns overlap, patchy involvement may become confluent producing lobar consolidation

Describe the stages of the inflammatory response seen in lobar pneumonia

Four stages

- Congestion - vascular engorgement, intra-alveolar fluid with few neutrophils and often the presence of numerous bacteria. The lung appears heavy, boggy and red
- Red Hepatisation - massive confluent exudation with neutrophils, red cells and fibrin filling the alveolar spaces, the lobe appears red, firm and airless with a liver, like consistency
- Gray hepatisation - progressive disintegration of red cells and the persistence of a fibrinosuppurative exudate, lobe appears greyish brown and dry surface.
- Resolution - exudate within the alveolar spaces undergoes progressive enzymatic digestion to produce granular semifluid debris that is resorbed, ingested by macrophages, expectorated or organised by fibroblasts growing into it.

What are the complications of pneumonia?

- Abscess formation - occurs as a result of tissue destruction and necrosis. Particularly common with type 3 pneumococci or klebsiella infection
- Empyema - spread of infection into the pleural cavity, causing intrapleural fibrinosuppurative reaction
- Bacteraemic dissemination - with seeding to heart valves, pericardium, brain, kidneys, spleen or joints causing metastatic abscesses, endocarditis, meningitis or other suppurative arthritis
- Local extension - pleuritis
- Bronchopleural fistula
- Parapneumonic effusion
- Respiratory failure/ARDS
- Pulmonary fibrosis
- Sepsis
- Death

9. Other Pneumonias

Describe the pathogenesis of aspiration pneumonia

- Aspiration of gastric contents
- Typically occurs in a patient with a decreased level of consciousness, abnormal swallow/gag reflex or repeated vomiting
- Chemical and bacterial contents
- Usually >1 organism (aerobes >anaerobes)
- Necrotizing
- High risk of progression to abscess formation or dissemination and death

What is atypical pneumonia?

A type of pneumonia characterised by interstitial pneumonitis, lack of exudate and a different clinical picture to typical pneumonia.

What organisms are usually involved?

- Mycoplasma
- Q fever (coxiella burnetii)
- Legionella
- Psittacosis (the bird one)
- Chlamydia
- Other viruses - RSV, parainfluenza, SARS, adenovirus

Describe the clinical features

- Usually less sputum
- No physical findings of consolidation
- Only a moderate increase in WCC
- Typical symptoms include fevers, myalgias, headache - cough is not prominent and is usually dry
- Has a lower mortality compared to typical or classic pneumonia

How is legionella contracted?

- Artificial aquatic environments e.g. water cooling tower, water supply tubing
- Inhalation of aerosol droplets
- Aspiration of contaminated drinking water

How is legionella diagnosed?

Urinary antigen PCR or the gold standard is sputum culture - done in a special medium

10. Tuberculosis

Describe the pathogenesis of tuberculosis in a previously unexposed immunocompetent person

- Infection by mycobacterium tuberculosis via airborne exposure
- The organism enters alveolar macrophages, which cannot digest it. It then replicates in the macrophages by blocking phagosome/lysosome fusion, leading to bacteraemia, which manifests as a mild flu-like illness or can be asymptomatic.
- There is a delayed hypersensitivity reaction, where T cells contribute to tissue destruction, granuloma formation and caseation
- The macrophage response also causes tuberculin positivity
- Re-exposure or reactivation causes a heightened immune reaction as well as tissue destruction
- The infection may be contained or may progress.
- It can reactivate with any form of immunosuppression from any cause.

Outline the natural history of TB infection

- Primary infection
- Primary complex (Ghon focus) of local caseation (the calcified scar from this infection is called the Ghon complex)
- It may heal OR become latent TB OR progressive primary TB
- If there is no clearance, reactivation or progression can lead to secondary TB
- Localised caseating lesions may form OR it may progress to secondary disease i.e. miliary TB

How may infection occur in secondary TB?

- May follow shortly after a primary infection (<5% of cases)
- Reactivation of latent organisms (occurs in areas of low disease prevalence)
- Reinfection (occurs typically in areas of high prevalence)

Describe the pathological features in the lung during secondary infection with TB

- Usually the lesion occurs in the apical upper lobe
- It is an area of inflammation/granuloma with multinucleate giant cells
- Typified by cavitation and caseous necrosis
- There is simultaneous healing with fibrosis and calcification

What are the complications of secondary TB?

- Tissue destruction
- Erosion of blood vessels
- Miliary TB spread
- Pleural effusion
- Empyema
- Fibrous pleuritis

Outline the diagnosis of TB

- Clinical features plus CXR changes
- Sputum microscopy x 3
- PCR
- Mantoux test