

Obstructive Lung Diseases: disease state characterized by airflow limitation that is not fully reversible.

- Emphysema
 - Chronic bronchitis
 - Asthma
 - Bronchiectasis
- } COPD
- ABCE

Emphysema: abnormal lung disease with abnormal irreversible dilatation of airspaces distal to terminal bronchiole $\Rightarrow$ destruction of airway walls

Classification: (according to its anatomic distribution)

① Centriacinar / Centrilobular Emphysema: dilatation of central/proximal parts of acini (distal alveoli are spared)

- $\rightarrow$ common in upper lobes (especially in apical segments)
- $\rightarrow$ Association — Heavy smokers — Coal-workers' pneumoconiosis — Chronic bronchitis
- $\rightarrow$ walls of emphysema show black pigment
- $\rightarrow$ inflammation around bronchi & bronchioles.

② Paracinar / Panlobular emphysema: all airspaces beyond terminal bronchioles are dilated

- $\rightarrow$ common in lower lobes, most severe at the bases
- $\rightarrow$ associated with α_1 -antitrypsin deficiency.

③ Distal acinar (Paraseptal) Emphysema: distal airspaces at periphery of lobule are dilated

- $\rightarrow$ dilated spaces of $> 1\text{ cm} \Rightarrow$ bullae
 - $\rightarrow$ bullae may rupture & cause spontaneous pneumothorax
 - $\rightarrow$ Common sites: adjacent to septa, pleura, margin of lobules; more severe in upper lobes
- ④ Irregular (scar/cicatrical) emphysema: acinus is irregularly involved
- $\rightarrow$ commonly found around old healed inflammatory processes like tuberculous scars.

Pathogenesis:

① Inflammatory mediators & leukocytes:

- Inflammatory mediators: from resident epithelial cells & macrophages
- Attraction of leukocytes

② Protease-antiprotease imbalance:

- inflammatory cells release proteases → damage connective tissue
- protease action is not prevented by antiproteases due to antiprotease deficiency & excess proteases

Genetic deficiency of α_1 -antitrypsin: gene on chromosome 14

⇒ inherited autosomal recessive disorder

⇒ excessive digestion of elastic tissues causes emphysema

③ Oxidative Stress: apoptosis of alveoli & inflammatory cells → oxidant production → further damage

④ Airway infection

→ obstruction of small airways in emphysema is due to:

- loss of elastic tissue in the walls of alveoli
- small airway inflammation

Gross: • upper 2/3 of lungs are more severely involved

- Irregular & distal acinar emphysema show bullae
- in advanced emphysema ⇒ voluminous lungs
- emphysema can easily be seen on cut-surface of formalin-inflated fixed lung

Microscopy: • abnormally large alveoli separated by thin septa

- destruction of alveolar walls
- enlarged pores of Kohn
- bullae may be seen
- inflammatory changes in small airways

Clinical Course: (manifestations appear late) B^2CD-w

- Cough & expectoration
- Weight loss
- Barrel-shaped chest
- Dyspnea with prolonged expiration
- Breathing through pursed lips

Complications: • Cor pulmonale • Congestive Heart Failure

- Cause of death: • Respiratory acidosis & coma • Right-sided heart failure
- Massive collapse of lungs secondary to pneumothorax

Other forms of Emphysema: $18C$

- Compensatory hyperinflation: dilation of alveoli without destruction of septal walls
→ compensatory response to loss of lung substance elsewhere
- Bullous emphysema: airspaces $> 1\text{cm}$ in diameter $\Rightarrow$ bullae or blebs
→ may rupture & produce pneumothorax
- Interstitial emphysema: entry of air into connective tissue stroma
→ results from alveolar tears in pulmonary emphysema during coughing

Chronic Bronchitis: persistent cough with sputum production for at least 3 consecutive months in at least 2 consecutive years

Etiology: • Cigarette smoking • Air pollutants • Toxic industrial inhalants • Respiratory tract infection

Pathogenesis: irritation by inhaled air pollutants → inflammation → infiltration by CD8+ T cells, macrophages, neutrophils → neutrophils release proteases → hyperplasia/hypertrophy of submucosal glands in large airways & marked increase of goblet cells in small airways → hypersecretion of mucus → mucus plugging of bronchial lumen → inflammation & fibrosis of bronchial wall → airway obstruction

Gross: Airway changes:

- Mucous membrane: appears dusky red due to hyperemia, swelling & edema
- Lumen: filled with mucus or mucopurulent secretions

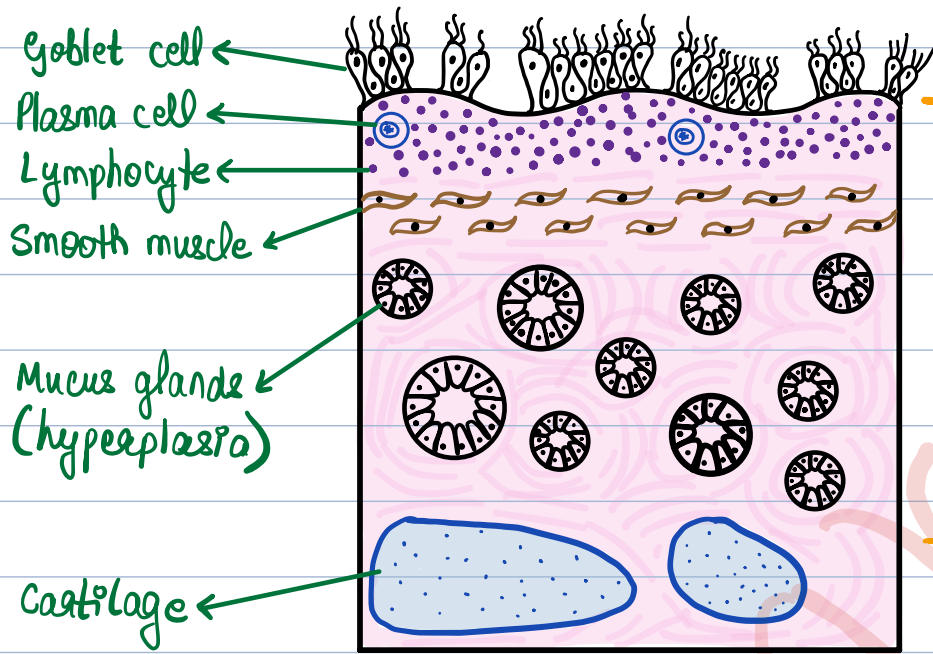
Microscopy: HR- msc

- Hyperplasia & hypertrophy of mucus-secreting glands in submucosa: shift of type of gland from normal mixed seromucous to pure mucus in trachea
→ increased in chronic bronchitis
- Reid index: ratio of thickness of mucus gland layer to thickness of wall between base of surface epithelium & inner limit of cartilage plates (Normal = 0.4)
- Chronic inflammation of airways with lymphocytic infiltration
- Surface epithelium: mild increase in number of goblet cells & focus of squamous metaplasia
- Marked narrowing of bronchioles: due to: i) excess mucus
ii) hyperplasia of glands, edema, inflammation, fibrosis
iii) obliteration of bronchial lumen due to fibrosis ⇒ bronchiolitis obliterans

Clinical Features: • persistent productive cough • dyspnea on exertion

- Blue bloaters ⇒ patients with hypercapnia, hypoxemia, mild cyanosis
- Pink puffers ⇒ patients have more emphysema than bronchial obstruction ∴ they hyperventilate to produce a normal blood gas profile

Complications: • COPD • Cor pulmonale • Squamous metaplasia & dysplasia



A
B

C
D

$$\left[\text{Reid index} = \frac{CD}{AB} \right]$$

Asthma: Chronic inflammatory disorder of bronchial tree in which breathing is periodically rendered difficult due to widespread narrowing of bronchi & increased mucus secretion
 ⇒ recurrent episodes of wheezing, breathlessness, tightness of chest, cough.

Classification:

WBC²

① According to type of antigen:

- Atopic / Allergic (extrinsic)
- Non-atopic (intrinsic)

② According to triggering agent/event:

- Seasonal
- Drug-induced
- Asthmatic bronchitis in smokers
- Exercise-induced
- Occupational

Atopic Asthma: • most common type • begins in childhood • family history is commonly present

- IgE-mediated Hs Rx
- Skin test with causative allergen results in an immediate wheal- & -flare reaction

Non-atopic Asthma: triggering event: respiratory infections due to viruses, inhaled air pollutants

Endogenous Risk Factors:

- ① Genetic predisposition
- ② Airway hyperresponsiveness
- ③ More common in boys than girls; after puberty, more common in women
- ④ < 25 years

Environmental Risk Factors:

P-AVDI

- ① Inhaled allergens
- ② Upper respiratory tract viral infections
- ③ Air pollutants
- ④ Passive smoking
- ⑤ Drugs (β -adrenergic blockers, aspirin)

Pathogenesis:

Hygiene hypothesis: individuals with lack of infections in early childhood are more prone to asthma

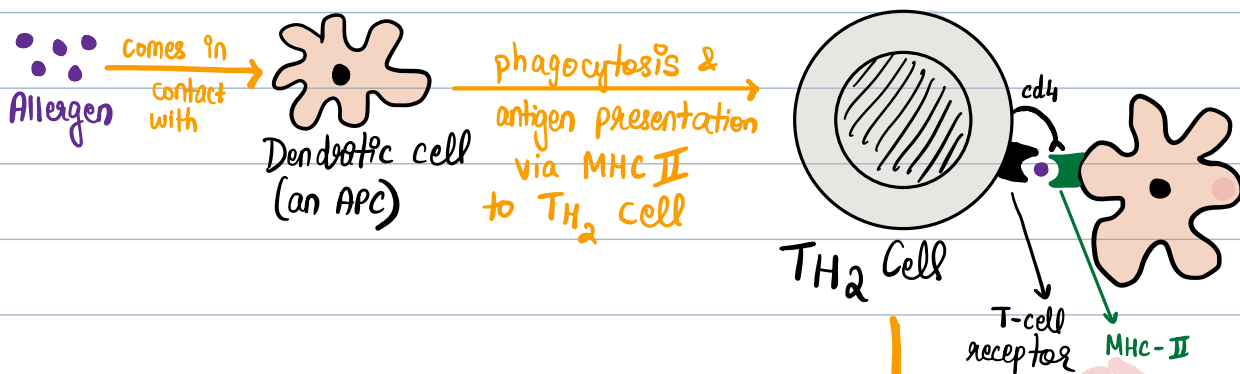
→ intestinal parasite infection may be associated with decreased risk of asthma

Major etiological factors in Atopic Asthma: ① Genetic predisposition to type I hypersensitivity (atopy)

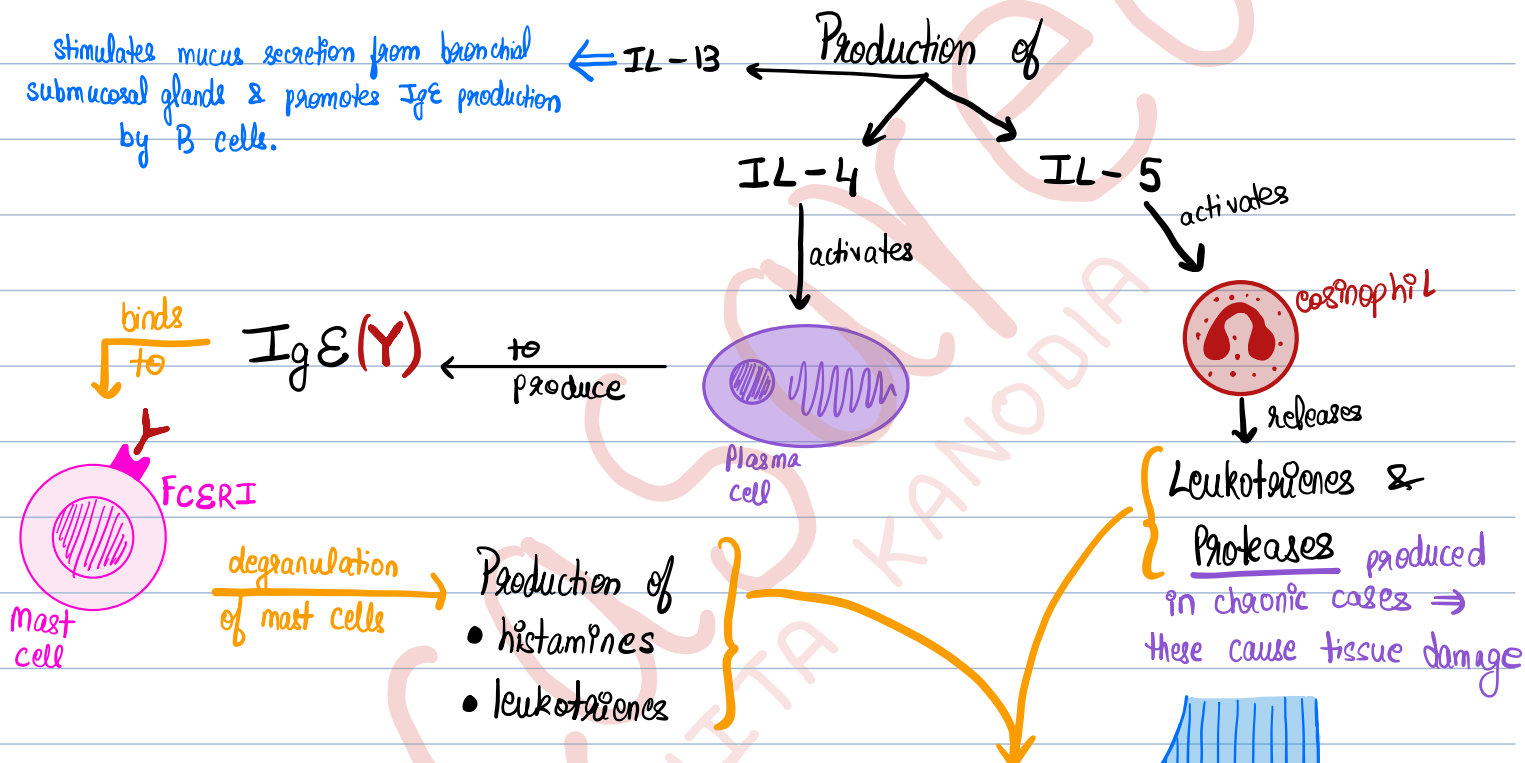
② acute & chronic airway inflammation

HAG

③ Hyperresponsiveness to environmental allergens



stimulates mucus secretion from bronchial submucosal glands & promotes IgE production by B cells.



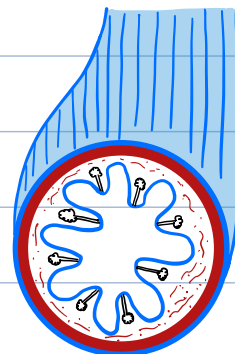
over chronic periods of exacerbation of asthma

- tissue becomes fibrotic
- thickening of the basement membrane

narrowing of airway

*
↓
reversible

- * Bronchoconstriction
- * increased mucous production
- * inflamed mucosa (due to fluid collection & immune cell infiltration)
- * increase in vascular permeability



permanently narrowed

*
↓
irreversible

Asthma is reversible *

Steps in Pathogenesis: Sensitization

[Inhaled allergens are taken up by APCs & elicit a T_H2 -dominated response favouring IgE production & eosinophil recruitment]



on Re-exposure, antigens bind to IgE bound on mast cells & release preformed mediators



Early phase reaction: — bronchoconstriction — increased mucous production

(produced directly by mediators from mast cells or by stimulation of vagal receptors in subepithelium)

— vasodilation with increased vascular permeability (causing edema)



Late-phase Reaction: — inflammation (leading to further narrowing of airways)

— airway remodelling.

Gross: ① Bronchi & bronchioles are occluded by plugs of thick mucus

② Patients who die due to status asthmaticus $\Rightarrow$ lungs are distended (due to overinflation) & shows small areas of atelectasis (collapse).

Microscopy: Air^2

① Increased amount of mucus forming mucus plugs: Mucus plugs contain desquamated epithelial cells & eosinophils

$\rightarrow$ formation of spiral-shaped casts of airways $\Rightarrow$ Curschmann spirals (may be found in sputum)

② Inflammation: numerous eosinophils in walls of airways

$\rightarrow$ Charcot-Leyden crystals: crystallized derived from eosinophil lysophospholipase binding protein called galectin-10

$\rightarrow$ edema & congestion of airways

③ Airway remodeling: structural changes in bronchial wall due to repeated bouts of inflammation:

i) Increase in number & size of submucosal glands

ii) hypertrophy &/or hyperplasia of bronchial wall smooth muscle

iii) increased vascularity

iv) deposition of subepithelial collagen & fibrosis

Clinical Course: acute asthma attack lasts for several hours

WBC^r

- chest tightness
- dyspnea
- wheezing
- cough with/without sputum

→ Status asthmaticus: most severe form of asthma

- severe acute paroxysm persists for days - weeks
- severe airflow obstruction ⇒ cyanosis, death.

Sputum findings: sputum is viscous & yellow & rich in eosinophils

→ Charcot - Leyden crystals

→ Curschmann spirals

→ Creola bodies (clusters of columnar epithelial cells shed from bronchus)

10:39

Bronchiectasis: abnormal dilation of bronchi & bronchioles $\Rightarrow$ either focal or diffuse

Etiology: caused by destruction of muscle & elastic tissue of bronchial wall

$\rightarrow$ Bronchiectasis $\begin{cases} \rightarrow \text{Obstructive} \\ \rightarrow \text{Nonobstructive (postinflammatory)} \end{cases}$

Nonobstructive (postinflammatory) Bronchiectasis: usually diffuse type with dilatation throughout the lung

$\rightarrow$ associated with chronic necrotizing infections

• **Kartagener's Syndrome / Immobile Cilia Syndrome (Primary ciliary dyskinesia):** autosomal recessive

$\rightarrow$ lack of ciliary function $\Rightarrow$ retention of infections $\rightarrow$ recurrent infections $\Rightarrow$ sinusitis, bronchiectasis, dextrocardia, male infertility

$\rightarrow$ genetic cause of bronchiectasis

• **Immunodeficiency:** hypogammaglobulinemia, HIV, bronchiolitis obliterans following lung transplantation

• **Autoimmune diseases:** rheumatoid arthritis, SLE, IBD

Obstructive Bronchiectasis: localised to obstructed segment of lung

Pathogenesis:

Partial/total obstruction of bronchial lumen

Chronic persistent necrotizing infection in bronchi

$\downarrow$
Impairs clearing mechanism of lung

$\downarrow$
Increased bronchial secretion

$\downarrow$
Accumulation of secretions distal to obstruction

$\downarrow$
Obstruction of airways by secretion

$\downarrow$
Secondary infection leads to inflammation

$\downarrow$
Inflammation & fibrosis of airway walls

$\swarrow \quad \searrow$
Weakening & dilatation of airway

$\downarrow$
Bronchiectasis

Classification:

I According to shape of bronchial dilation:

- ① Saccular (cystic) bronchiectasis
- ② Cylindrical (tubular) bronchiectasis
- ③ Fusiform
- ④ Varicose

II According to extent of involvement:

- ① Generalized: usually bilateral, commonly affects lower lobes, left lobe is more commonly involved
- ② Localised: restricted to a single segment of lung

Gross:

- ① bronchi & bronchioles are dilated & can be traced upto pleural surfaces
- ② Cut-surface: wall of bronchi is thickened by fibrosis & lumen is filled with thick, mucopurulent secretions

Microscopy:

I Bronchial Wall:

- ① Dilatation of bronchi & bronchioles & destruction of their wall
- ② Dense infiltration of chronic inflammatory cells within walls of airways
- ③ Fibrosis of airway walls in chronic cases

II Mucosal changes:

- ① Desquamation of lining epithelium with areas of ulceration
- ② Lining columnar cells show pseudost stratification & squamous metaplasia in surrounding epithelium

Clinical Course:

- ① severe persistent productive cough
- ② foul-smelling sputum (sometimes bloody)
- ③ Symptoms are precipitated by upper respiratory tract infections
- ④ Paroxysms of cough occur when patient rises in the morning (occurs due to change in position leading to drainage of collections of pus & secretions into bronchi)

Lobar Pneumonia: usually affects the lower lobes

→ Morphological Stages: Congestion, Red hepatization, Grey hepatization, Resolution

Congestion: lasts for < 24 hours

Gross: involved lobe is heavy, boggy & red

→ blood-stained frothy fluid oozes from cut-surfaces

Microscopy: ① Dilatation & congestion of capillaries in alveolar walls

② Alveoli are filled with pale eosinophilic fluid with neutrophils, red cells & bacteria

Red Hepatization: lasts for 2-3 days

Gross: lobe appears red, firm & airless (firm consistency of affected lobe of lung resembles that of liver)

→ pleura may show serofibrinous pleurisy

→ Cut-section: red, granular

Microscopy: ① alveoli show exudate & interlacing strands of fibrin

② Numerous neutrophils & red cells are found in fibrin meshwork

Gray Hepatization: seen on 5-7 days

Gross: gray appearance of affected lobe

→ cut-surface: dry, gray, granular

Microscopy: ① progressive disintegration of red cells

② fibrinosuppurative exudate in alveoli in which neutrophils are replaced by macrophages

③ clear space between alveolar wall & exudate due to contraction of fibrin thread

Resolution: occurs by liquefaction of previously solid, fibrinous constituents of exudate

→ liquefaction is due to fibrinolytic enzymes liberated from neutrophils

→ liquefied material is removed partly by expectoration & partly by ingestion by macrophages & drained through lymphatics

Gross: affected lobe becomes more crepitant; cut-section appears frothy

Microscopy: alveolar spaces show granular material & semifluid debris.

Bronchopneumonia: widespread focal/patchy areas of acute suppurative inflammation

Gross: ① Involved alveoli show consolidation

② consolidated areas are larger & more numerous in lower lobes

③ Cut-section: appears slightly raised above surface of surrounding lung

↳ dry, solid, granular, gray-red to yellow, poorly delimited at their margins

Microscopy: bronchi, bronchioles & alveolar spaces are filled with exudate rich in neutrophils.

Complications of Pneumonia: ① Lung abscess

② Organization: ingrowth of granulation tissue into alveolar exudate → gradual increase in alveolar fibrosis leads to a shrunken & firm lobe ⇒ called carnification.

③ Pleuritis, pleural effusion, pyothorax, empyema

④ Bacterial dissemination (bacteremia): • Endocarditis • Pericarditis • Meningitis

• Suppurative arthritis • Metastatic abscesses in kidneys or spleen

Clinical Features: • sudden onset of high fever, chills, cough with mucopurulent sputum

• involved lobe appears radiopaque on radiography

	Lobar Pneumonia	Bronchopneumonia
Definition	Diffuse inflammation affecting the part or entire lobes	widespread focal/patchy areas of acute suppurative infection of terminal bronchioles extending into adjacent alveoli
Age group	More common in adults	Develops at extremes of age (infants & old age)
Predisposing factors	Usually develops in healthy individuals	Usually accompany pre-existing diseases
Causative organism	Pneumococci, Klebsiella pneumoniae, Staphylococci, streptococci	Staphylococci, streptococci, Pseudomonas, Haemophilus influenzae
Pathologic features	4 stages — Congestion, Red hepatization, gray hepatization, Resolution	Patchy consolidation, bronchi, bronchioles, adjacent alveoli are filled with neutrophilic exudate
Blood Findings	Neutrophilic leucocytosis & positive blood culture	Neutrophilic leucocytosis & positive blood culture
X-ray	Shows consolidation	Shows mottled focal opacities
Complications	less common — pleural effusion, empyema, lung abscess	Bronchiectasis, pleural effusion, empyema, lung abscess
Response to treatment	Better	Variable
Prognosis	Good	Poor

Tuberculosis: (aka Koch's disease) — communicable, chronic granulomatous disease
caused by *Mycobacterium tuberculosis*

Characteristics of Mycobacteria:

Coal Workers' Pneumoconiosis: (CWP) $\Rightarrow$ parenchymal lung disease

caused by inhalation of carbon particles (coal mine dust)

$\rightarrow$ causes a group of diseases called **Black Lung**

$\rightarrow$ Lung lesions are divided into 3 stages:

① Pulmonary Asymptomatic Anthracosis: harmless coal-induced lesion in lungs

$\rightarrow$ Inhaled carbon is engulfed by macrophages present in alveoli $\rightarrow$ accumulate in connective tissue $\rightarrow$ carried by lymphatics to regional lymph nodes

② Simple CWP with Little/No Pulmonary Dysfunction:

Gross: $\rightarrow$ Coal macule: characteristic non-palpable lesion

$\rightarrow$ Coal nodule: larger, palpable, firm lesion

$\rightarrow$ Both are mainly seen in upper lobes & upper zones of lower lobes

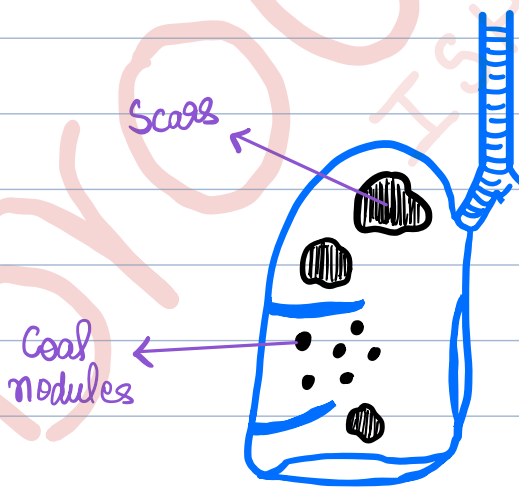
Microscopy: Coal macule: focal collection of many carbon-laden macrophages surrounding respiratory bronchiole

Coal nodule: carbon-laden macrophages + collagen & reticulin fibers

③ Complicated CWP (Progressive Massive Fibrosis - PMF):

Gross: multiple, dark, black scars $> 2\text{cm}$

Microscopy: carbon pigment + carbon-laden macrophages + dense collagen + disrupted lung architecture



{ Caplan Syndrome: coexistence of
rheumatoid arthritis with
pneumoconiosis }

Silicosis: parenchymal lung disease associated inhalation of crystalline silicon dioxide (silica)

Susceptible individuals:

- Sandblasters
- Stone cutters
- Ceramic manufacturing workers
- Cleaning of boilers

Pathogenesis: quartz is the most common cause of silicosis

→ inhaled particles reach the lungs → particles reach alveoli → interact with alveolar epithelial cells → ingested by alveolar macrophages → activation of macrophages → release of mediators → stimulate fibroblast proliferation & collagen formation

Cyross:

① **Simple Nodular Silicosis:** tiny, barely palpable, pale to blackened silicotic nodules in upper zones

→ enlargement of hilar lymph nodes

→ periphery of lymph node shows thin rim of calcification (seen radiographically as eggshell calcification)

② **Progressive Massive Fibrosis:** expansion & coalescence of lesions

→ defined radiologically as nodular masses > 2cm diameter in a background of simple silicosis

→ lesions are hard; may undergo central softening & cavitation

Microscopy:

Silicotic nodule: wheeled appearance

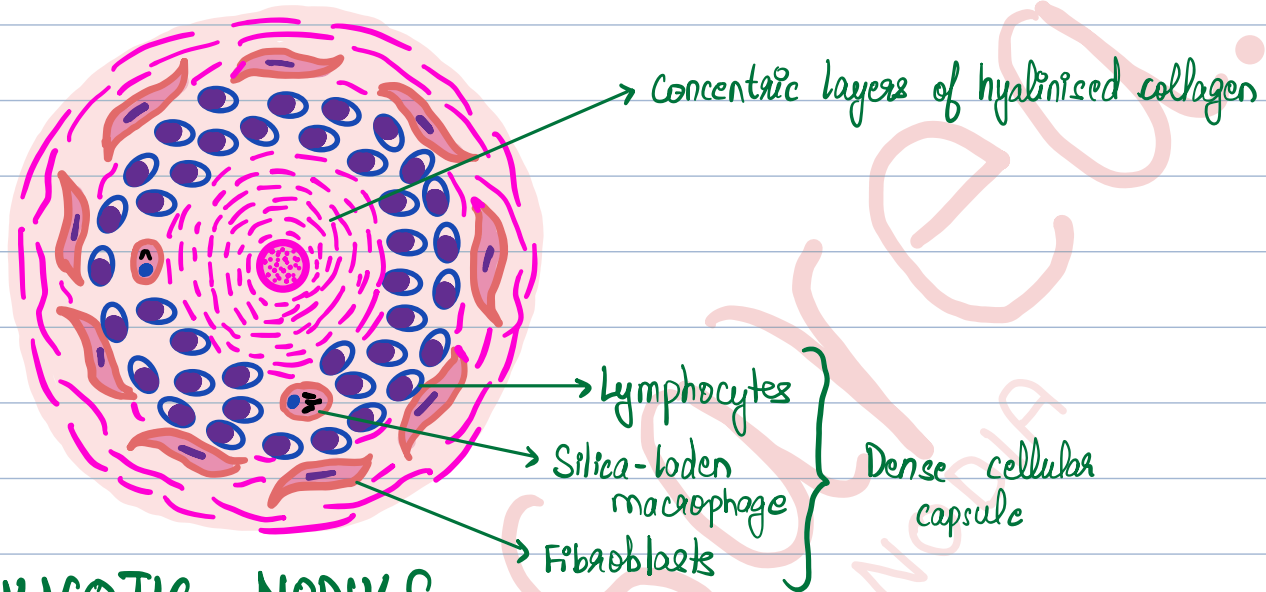
→ **Center:** concentric layers of hyalinized acellular collagen surrounded by dense cellular capsule of condensed collagen

→ **Periphery:** aggregates of lymphocytes, silica-laden macrophages & fibroblasts

Polarised light microscopy: birefringent silica particles in centre of silicotic nodule

Clinical Course: Simple nodular silicosis $\Rightarrow$ lung functions are normal/moderately affected

PMF $\Rightarrow$ shortness of breath, increased susceptibility to lung infections



SILICOTIC NODULE

Asbestosis: interstitial fibrosis of lung caused by exposure to asbestos dust

↳ Asbestos types: Serpentine & amphibole form

Serpentine form: chrysotile (white asbestos)

↳ long, wavy, flexible structure likely to become impacted in upper RT & removed by mucociliary action

Amphibole form: crocidolite (blue asbestos) & amosite (brown asbestos)

↳ straight, rigid, brittle fibers that may align themselves in airstream & remain stable in lung

→ more pathogenic than chrysotiles

Pathogenesis: Inhaled asbestos fibers reach air spaces → macrophages attempt to ingest & clear fibers → activation of macrophages → release chemotactic & fibrogenic mediators → generalised interstitial pulmonary inflammation & interstitial fibrosis

→ Asbestos acts as a tumor initiator & promoter

→ Asbestos produces reactive free radicals

Course: ① lesions begin in lower lobes & subpleura

② Early stages: interstitial fibrosis around respiratory bronchioles & alveolar ducts ⇒ mineral dust-induced small airways disease.

③ Late stages: interstitial fibrosis becomes more extensive & may involve entire lung

→ normal architecture of lung is disrupted ⇒ dilated air spaces (cystic spaces) surrounded by thick fibrous walls → Honeycombed appearance → lungs become small

Microscopy:

Asbestos Bodies: translucent centers of asbestos fibers coated with a film of protein rich

in iron • golden-brown • fusiform / beaded rods • coating is thickest at both ends of fibers ⇒ dumbbell appearance

• formed when macrophages attempt to phagocytose asbestos fibers

Pleural Plaques: most common manifestation of asbestos exposure

Gross: pearly-white, well-circumscribed • usually bilateral • most frequent on anterior & posterolateral aspects of parietal pleura & over dome of diaphragm

Microscopy: acellular, dense, hyalinised fibrous tissue with many slit-like spaces arranged parallelly $\Rightarrow$ basket-weave pattern

Clinical Features: • dyspnea on exertion initially, later seen even at rest • productive cough
• chest X-ray: irregular linear densities, particularly in both lower lobes • may progress to respiratory failure, cor pulmonale & death

[5:16]

Lung Carcinomas: most common cause of cancer death

↳ mainly due to carcinogenic effects of cigarette smoking

→ Age: 50-80 years ; more common in males

Etiopathogenesis:

• Tobacco Smoking:

Constituent in tobacco smoke	Effect
• Tar • PAH • Nicotine	Carcinogenesis
• Nitrosamine • Benzopyrene • Phenol	Tumor promotion

- Ionizing radiations
- Chromium, nickel
- Vitamin A deficiency
- Genetic predisposition (polymorphism of CYP1A1 gene)
- Uranium
- Atmospheric pollution
- Idiopathic pulmonary fibrosis
- Asbestos
- Heredity

Genetics:

① Squamous cell Carcinoma:

i) Inactivation of tumor suppressor gene: • chromosome deletions involving 3p, 9p (site of CDKN2A gene) & 17p (site of TP53 gene)

- Loss of retinoblastoma (RB) tumor suppressor gene

ii) Activation of oncogenes: • Amplification of FGFR1 & MET

- Mutations in EGFR, KRAS, BRAF, ERBB2.
- Translocations - eg: ALK, ROS1, RET.

② Small Cell Carcinoma:

i) Inactivation of tumor suppressor gene: TP53, RB, chromosome 3p deletion

ii) Activation of oncogenes: amplification of genes of MYC family

③ Adenocarcinoma:

i) Activation of oncogenes: • gain-of-function mutation in EGFR, BRAF, RET, MET, ERBB2/HER2, ALK

- mutations in KRAS gene

Classification of Lung Tumors:

I Epithelial tumors:

① Malignant tumors:

i) Squamous cell carcinoma

ii) Adenocarcinoma

- Preinvasive lesions: Atypical adenomatous hyperplasia, adenocarcinoma in situ (non-mucinous/mucinous)
- Minimally invasive adenocarcinoma (MIA)
- Invasive: Lepidic, acinar, papillary, micropapillary, solid

iii) Neuroendocrine tumors:

- Small-cell carcinoma
- Large-cell carcinoma
- Carcinoid tumors: typical & atypical

iv) Large cell carcinoma

v) Mixed carcinomas - Adenosquamous carcinoma

- Combined small cell carcinoma

vi) Carcinomas with pleomorphic, sarcomatoid, sarcomatous elements

② Benign tumors: i) Squamous papilloma ii) Adenoma

II Mesenchymal tumors:

① Pulmonary hamartoma

② Chondroma

③ Fibromatous tumors

III Lymphohistiocytic tumors

IV Tumors of ectopic origin

V Metastatic tumors

²
MELT

ML
SCAN

Sites of Lung Cancer:

- Central (hilus): cancers arising in & around the hilus of lung
- Peripheral: cancers arising from alveolar septal cells or terminal bronchioles

Squamous Cell Carcinoma:

Gross: ① Most tumors arise in central portion of lung from major bronchus

i) Peribronchial growth: tumor penetrates bronchus wall & infiltrates along peribronchial tissue

ii) Intraparenchymal growth: tumor grows as a cauliflower-like mass which pushes surrounding lung substance

iii) Exophytic growth: projects into lumen of bronchus (intraluminal mass) & obstructs the bronchus causing atelectasis & infection distal to obstruction

② Gray-white, firm to hard consistency

③ Cut-section: shows focal areas of haemorrhage & necrosis with yellow-white mottling & softening.

Microscopy: ① Keratinization: - epithelial keratin pearls

- individual cell keratinization

② Intercellular bridges: seen as slender gaps between adjacent cells

Grades: on the basis of amount of keratinization:

i) Well-differentiated: show keratin / squamous pearls $\Rightarrow$ small round nests of brightly eosinophilic aggregates of keratin surrounded by concentric (onion skin) layers of squamous cells

ii) Moderately differentiated: show individual cell keratinization $\Rightarrow$ cells with intensely eosinophilic glassy & dense cytoplasm

iii) Poorly differentiated: only intercellular bridges are seen with higher mitotic activity

Adenocarcinoma In Situ (AIS):

Gross: ① seen in terminal bronchioalveolar regions

② seen in peripheral portions of lung as a single nodule (coin lesion)

Microscopy: ① pure bronchioalveolar growth pattern

② they grow along pre-existing alveolar walls without destruction of alveolar architecture $\Rightarrow$ lepidic growth pattern (neoplastic cells resemble butterflies sitting on a fence)

Subtypes:

i) Nonmucinous: columnar, peg-shaped or cuboidal cells

ii) Mucinous: tall columnar cells with cytoplasmic & intra-alveolar mucin

iii) Mixed: nonmucinous + mucinous.

Invasive Adenocarcinoma: classification

- lepidic
- acinar
- papillary
- solid
- micropapillary

Gross: ① usually peripherally located & smaller

② irregular masses of 2-5 cm diameter

③ Cut-section: Nonmucinous $\Rightarrow$ grayish-white
Mucinous $\Rightarrow$ glistening / gelatinous

Microscopy: $\rightarrow$ Most tumors are positive for thyroid transcription factor-1 (TTF-1).

i) Lepidic: lepidic growth pattern

ii) Acinar: regular glands lined by cuboidal / columnar cells

iii) Papillary: single cell layer covers a fibrovascular connective tissue core

iv) Micropapillary: small papillary tufts of tumor cells without fibrovascular core

v) Solid: poorly differentiated

Small Cell Carcinoma: (aka oat cell carcinoma) $\Rightarrow$ tumor cells arise from neuroendocrine progenitor cells in bronchial epithelial lining.

Gross: may arise in major bronchi (central) or in peripheral regions

Cut-section: soft, friable, white with extensive haemorrhage & necrosis

Light Microscopy: ① Small round / fusiform cells

② Scanty cytoplasm with ill-defined borders

③ hyperchromatic nucleus with finely granular chromatin (salt & pepper pattern) & nuclear molding

④ inconspicuous / absent nucleoli

⑤ high mitotic count

⑥ Cells are fragile & show fragmentation & crush artifact

⑦ Cells grow in sheets or clusters

⑧ Necrosis is common & extensive $\rightarrow$ blood vessel may stain blue due to deposition of DNA from necrotic tumor cells $\Rightarrow$ Azoparado's effect

Electron Microscopy: membrane-bound neurosecretory granules are seen.

Large Cell Carcinoma:

Gross: generally arises in periphery of lung

$\rightarrow$ spherical tumor with well-defined borders

$\rightarrow$ Cut-section: bulging, fleshy, homogenous appearance

Microscopy: large tumour cells, moderate amount of cytoplasm, large nuclei, prominent nucleoli, vesicular chromatin.

Carcinoid Tumors: low-grade malignant epithelial tumors

→ tumor cells arise from neuroendocrine progenitor cells in bronchial epithelial lining.

→ Common < 40 years

Gross: tumors arise centrally or peripherally

i) Central tumors: finger-like or spherical polypoid masses covered by intact mucosa

→ they project into bronchial lumen as endobronchial lesion

→ some may penetrate bronchial wall to enter peribronchial tissue ⇒ collar-button lesion

ii) Peripheral tumors: solid & nodular

Microscopy: subclassification: i) Typical: < 2 mitoses / 10 high-power fields

ii) Atypical: 2-10 mitoses / 10 high-power fields

Clinical features: ① intraluminal growth ⇒ dyspnea, bronchiectasis, emphysema, atelectasis

② Metastasis & secretion of vasoactive amines ⇒ Carcinoid syndrome (intermittent attacks of diarrhea, flushing, cyanosis)

Local Effects of Lung Cancer:

Pathologic basis	Effects
Obstruction of airway by tumor	Pneumonia, abscess, atelectasis, focal emphysema
Local spread into pleura	Pleuritis & effusion
Local spread to pericardium	Pericarditis, effusion, tamponade
Compression of SVC by tumor	Superior vena cava syndrome
<u>Invasion of</u> :	
Recurrent laryngeal nerve	Hoarseness
Phrenic nerve	Diaphragm paralysis
Sympathetic ganglia	Horner Syndrome
Esophagus	Dysphagia
Chest wall	Destruction of rib

Spread of Lung Cancer:

- ① Local spread: to pleural surfaces, pleuritis, pericarditis
- ② Lymphatic spread: to tracheal, bronchial, hilar & mediastinal lymph nodes
- ③ Hematogenous spread: to adrenals, liver, brain, bone

Paraneoplastic Syndromes in Lung Cancer:

Elaborated hormone or factor	Effects
Antidiuretic hormone (ADH)	Hyponatraemia
ACTH	Cushing syndrome
Parathormone, parathyroid hormone - related peptide	Hypercalcaemia
Calcitonin	Hypocalcaemia
Gonadotropins	Gynecomastia
Serotonin & bradykinin	Carcinoid Syndrome