Drug & Radiation induced lung diseases

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- Drug-induced lung diseases have been a challenge since the dawn of modern medicine
- 1880, William Osler suggested a pathophysiologic relationship of pulmonary edema associated with opiate exposure
- 1972, Edward Rosenow identified 20 drugs that clearly caused pulmonary toxicity

Rosenow EC. Ann Intern Med 1972; 77:977–991

- Cooper et al expanded the list to 37 drugs a decade later

- Presently > 350 drugs have been implicated in causing pulmonary manifestations
- Number of drugs will continue to grow as new agents & biological response modifiers are developed
- Involve all components of respiratory system

- Epidemiology of DILD is not firmly established as it is diagnosis of exclusion
- No pathognomonic clinical, laboratory, physiologic, radiographic, or histologic findings
- Most reactions are idiosyncratic without any clear relationship to dose / time of exposure
- Drugs can cause toxicity years after exposure → cyclophosphamide

- Risk factors poorly defined
- Confounding variables
  - Use of other drugs
  - Oxygen
  - Radiation therapy

  can cause pulmonary injury or have interactive effects & hamper diagnosis
- Rechallenge with implicated drug is rarely performed as effective alternative agents are usually available

- Thorough drug exposure history, high index of suspicion & use of systematic diagnostic is required

- Management is largely supportive
  - Therapy with implicated drug is withdrawn
  - Trial of corticosteroids is considered if
    - Significant symptoms
    - Gas-exchange abnormalities
- Scientific basis for corticosteroids is supported by anecdotal reports w/o well designed controlled studies

Table 1. *Major Clinical Syndromes of Drug-Induced Pulmonary Disease*

1. Chronic pneumonitis/fibrosis*
2. Hypersensitivity-type lung disease*
3. Acute noncardiogenic pulmonary edema*
4. Bronchiolitis obliterans with organizing pneumonia
5. Alveolar hypoventilaton
6. Bronchospasm
7. Cough
8. Concentric bronchiolitis obliterans
9. Pleural effusions
10. Venous thromboembolism
11. Pulmonary vasculitis
12. Pulmonary hypertension
13. Drug-induced SLE
14. Alveolar hemorrhage
15. Pulmonary renal syndrome
16. Alveolar proteinosis
17. Mediastinal abnormalities (*eg*, adenopathy, lipomatosis, or mediastinitis)
18. Panlobular emphysema
19. Pulmonary calcinosis
20. Pseudosepsis syndrome

*Most common pulmonary manifestations.

ACCP Pulmonary Med Brd Rev 2009 ; 319-344

Chronic Pneumonitis/Fibrosis

- Most common manifestations
- Present with insidious onset of cough & dyspnea
- Weight loss & clubbing may also be present → possibility of an underlying malignancy or IPF

- CXR & HRCT:
  - Reticular infiltrates - in basilar subpleural regions and progressing to diffuse disease

- PFTs
  - Reduced lung volumes & DLCO
  - Arterial hypoxemia at rest / with exercise

Table 2. *Some Drugs That Cause Chronic Pneumonitis/Fibrosis*

Chemotherapeutic Agents	Nonchemotherapeutic Agents
• Azathioprine	• Amiodarone*
• BCNU	• Anti-TNF-α-targeted therapy
• Bleomycin*	• Cocaine
• Busulfan	• Gold
• Chlorambucil	• Heroin
• Cyclophospamide	• Methysergide
• Fludarabine	• Nitrofurantoin
• Gemcitabine	• Penicillamine
• 6-Mercaptopurine	• Phenytoin
• Methotrexate	• Sirolimus
• Mitomycin C	• Statins
• Taxanes (paclitaxel/ docetaxel)	• Sulfasalazine
• Tyrosine kinase inhibitors (imatinib)	• Tocainide

*Most commonly implicated.

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Hypersensitivity-Type Lung Disease

- Any drug can cause reaction with respiratory symptoms associated with PIE
- Methotrexate & Antibiotics (β-lactam & sulfa-containing)
- Patients can present
  - Acute onset → Loeffler syndrome - cough, dyspnea, fever, rash, myalgias, peripheral eosinophilia, and fleeting infiltrates
  - Subacute → CEP as low-grade fever, night sweats, nonproductive cough & weight loss
- Diagnosis → challenging as peripheral eosinophilia not seen in every pt
- FOB with BAL & biopsy or prompt response to corticosteroids favours
- Prognosis is favorable with a mortality rate of 1%

Noncardiogenic pulmonary edema

- No. of drugs causes NCPE
- Acute dyspnea & nonproductive cough
- CXR - diffuse acinar and/ or ground-glass infiltrates
- Histopathology can be similar to ARDS

- Mechanisms
  - ↑ filtration coefficient of respiratory membrane → making it more permeable
  - Depress CNS resulting in neurogenic PE
  - Idiosyncratic reaction within hours of absorption

- Prognosis depends on offending agent
  - overdose of salicylates is potentially reversible
  - carmustine-induced generally have a poor prognosis

Cryptogenic Organizing Pneumonia

- Presentation → cough, dyspnea & crackles on physical examination
- CXR - patchy airspace infiltrates
- PFT - mixed obstructive and restrictive defect

- Gold and penicillamine – used for management of RA
- Difficult to distinguish drug-induced COP from underlying CVD
- Management :
  - High clinical suspicion
  - Lung biopsy
  - Prompt withdrawal of therapy
  - Administration of corticosteroids
- Outcome is generally favourable

Alveolar Hypoventilation

- Drugs that induce respiratory depression or block respiratory muscle function

- Pulmonary or neuromuscular disorders are prone to develop acute hypercarbic RF

- Aminoglycoside-induced neuromuscular blockade → rare potentially life-threatening → exposed to neomycin, streptomycin, tobramycin, gentamicin, amikacin, kanamycin, and netilmicin

- Risk is ↑ in presence of
  - Disease / drug that promotes neuromuscular blockade
  - ↑ aminoglycoside drug levels
  - Hypomagnesemia
  - Hypocalcemia

- Mx requires high clinical suspicion & withdrawal of drug to avoid further RF

Bronchospasm

- Presentation: wheezing, cough, dyspnea
- Spirometry → airways obstruction
- Mechanism varies with agent
- Asthma →β-adrenergic blockers induce bronchospasm within minutes by inhibition of adrenergic bronchodilator tone
- Any route of administration can induce bronchospasm

- Aspirin → mediated by an enhanced 5-lipoxygenase pathway
  - production of bronchoconstricting cysteinyl leukotrienes
  - reduction in bronchodilating prostaglandins E2

- Dipyridamole →augments levels of adenosine → bronchoconstrion

- Gold /penicillamine → irreversible airways obstruction due to concentric bronchiolitis obliterans

Isolated Cough

- Most common manifestations of DILD
- Mechanism → vagus nerve-mediated reflex caused by chemical & mechanical stimuli in upper & LRT
- ACE inhibitors → 10% of patients induce isolated nonproductive cough without associated bronchospasm / parenchymal disease

J Respir Dis 1997; 18:762–768

Pleural Effusions

- Less common as compared to parenchymal
- Acute onset seen as part of
  - hypersensitivity reaction after exposure to amiodarone, methotrexate, and nitrofurantoin
  - SLE-like reaction
- Anticoagulants →induce acute hemorrhagic effusion
- Chronic pleural effusion
  - Long-term exposure to drugs that induce DHT response (methotrexate / procarbazine*)*
  - Association with development of interstitial pulmonary inflammation/fibrosis (busulfan / methotrexate)

Pulmonary Vascular Disease

Table 9. *Some Drugs That Cause Pulmonary Vascular Disease*

Complication	Chemotherapeutic Agents	Nonchemotherapeutic Agents
Thromboembolic disease		Estrogens/hormonal treatment Phenytoin Steroids
Pulmonary hypertension	Mitomycin IL-2	Aminorex (recalled) Amphetamines Dexfenfluramine (recalled) Fenfluramine (recalled) L-tryptophan (recalled) Oral contraceptives
Vasculitis	Busulfan	Cocaine/heroin Nitrofurantoin Zafirlukast/montelukast
Veno-occlusive disease	Bleomycin Busulfan BCNU Mitomycin	Oral contraceptives

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Miscellaneous Drug-Induced Pulmonary Reactions

lupus erythematosus

- SLE accounts for 5 to 12 % of all cases
- 90% caused by Hydralazine, Procainamide, INH, Penicillamine & Quinidine

- Anti TNF targeted therapy (etanercept, infliximab, & adalimumab)

- Hydralazine & INH - SLE occur more frequently in slow acetylators
- 20% of patients receiving doses of 400 mg/d of Hydralazine develop SLE

- Procainamide-induced SLE is time related
  - 50% develops + ve ANA in ~ 3 months
  - nearly all patients by 1 year

- Drug -induced SLE - negative for dS DNA

- CXR → PE, atelectasis, diffuse interstitial & alveolar infiltrates
- Alveolar hemorrhage syndrome is not a feature

- Drug withdrawal results in prompt resolution of symptoms within days
- CS occasionally required for symptomatic relief

Alveolar hemorrhage and hemoptysis

- Penicillamine can cause pulmonary-renal syndrome similar to Goodpasture syndrome
- Oral anticoagulants can induce spontaneous pulmonary hgs with in days to years
- Abciximab → Ab directed against platelet glycoprotein IIb/IIIa receptor can cause severe alveolar Hgs

- Relatively rare complication [0.3%]
- Presentation within hrs to 2 days after the first dose

Chest 2001; 120:126–131

- Bevacizumab →monoclonal Ab against VEGF can result in fatal pulmonary hemorrhage

N Engl J Med 2006; 355:2542–2550

- Drug therapy withdrawal is usually sufficient in anticoagulant induced bleeding
- Role of factor VIIa is not established

- DAH with extensive or persistent bleeding, or evidence for renal failure → CS or immunosuppressive agents

Clin Chest Med 2004;25:133– 40

Mediastinal abnormalities

- **Phenytoin** can induce a pseudolymphoma syndrome → a/w peripheral & rarely mediastinal adenopathy
- **Methotrexate** → transient hilar adenopathy during hypersensitivity-type response which regresses 1 to 2 weeks after drug withdrawal
- **Corticosteroids** → Mediastinal fullness due to lipomatosis
- Mediastinitis associated with fever & chest pain →rarely seen after esophageal variceal **sclerotherapy**

- Other rare pulmonary adverse drug effects reported :
  - Busulfan-induced alveolar proteinosis
  - Methylphenidate-induced panlobular emphysema
  - Pulmonary parenchymal Ca deposition associated with → antacids, calcium, high-dose vitamin D
- Long-term salicylate ingestion can cause a pseudosepsis syndrome

Chemotherapy-Associated Pulmonary Toxicity

- Azathioprine - purine analog that inhibits DNA synthesis
- Immunosuppressive agent in Tt of IPF & organ transplantation

- Mercaptopurine → active metabolite of azathioprine & is an antineoplastic agent

- About 1% cases causes pulmonary fibrosis, hypersensitivity-type reactions/PIE or DAD

BCNU

- Extensively studied member of nitrosourea
- Active against various neoplasms including CNS as it can cross blood-brain barrier
- Causes IPF & granulomatous inflammation that can progress after drug withdrawal

- Promotes oxidant-induced lung injury by inhibiting glutathione reductase
- Cytotoxic changes are characterized by
  - Alveolar T2 hyperplasia and dysplasia
  - Fibroblastic foci of proliferation
  - Interstitial fibrosis

- Symptom onset highly variable→ days to as many as 17 yr.
- Insidious onset of nonproductive cough dyspnea
- CXR→reticular nodular interstitial infiltrates
- Risk factors include →total dose, other agents & preexisting lung disease
- Incidence
  - high-dose (1,500 mg/m2)→ 20 to 50%
  - low-dose →1 to 5%
- Cyclophosphamide & radiation ↑ risk without synergistic effect
- Mortality rate nearly 90% & Corticosteroid therapy no role in prevention

Bleomycin

- Cytotoxic antibiotic isolated from *Streptomyces verticillus*
- Used in head & neck carcinomas, germ-cell tumors, Hodgkin and NHL
- Accumulates in skin & lung → skin ulcerations & PF

- Overall
  - Incidence 10% (3 to 40%)
  - Fatal in 1 to 2%
- Binds to intracellular iron in alveolar epithelial and vascular endothelial cells & generates highly ROS(hydroxyl radicals) in presence of O_2

- 3 major clinical manifestations
  - chronic interstitial fibrosis
  - hypersensitivity-type disease
  - COP

- Interstitial fibrosis is seen in approximately 11%

- Risk factors for the development of bleomycin induced pulmonary toxicity include
  - Total dose: incidence of 3 to 5% - 300 U but 20% - 500 U
  - Oxygen: synergistic toxic interaction even yrs after exposure

    FiO_2 of pt who have ever received bleomycin should be kept 25%
  - Radiation: ↑ risk even years after exposure
  - Age: > 70 years
  - Abnormal renal function
  - Concurrent use of other cytotoxic agents : cyclophosphamide, doxorubicin, G-CSF, methotrexate, and vincristine

Busulfan

- Alkylating agent →Ch myeloproliferative disorders
- First chemotherapeutic agent implicated in causing chronic pneumonitis/pulmonary fibrosis
- Synergistic damage with O_2 / radiation / cytotoxic drugs
- Incidence
  - symptomatic pulmonary fibrosis is ~ 4 to 5%
  - Asymptomatic - up to 46%
- A threshold dose has not been established

- C/F: insidious onset > 3 years after initiating therapy →cough, dyspnea, fever, malaise, weight loss
- PFT - Restrictive /↓ Dlco

- CXR :
  - Diffuse interstitial and alveolar infiltrates with a basilar predominance
  - Occasionally → pleural effusion / nodular densities
  - Normal

- Mx → drug withdrawal & corticosteroids
- Prognosis is poor with mortality rate ranging from 50 to 80%
- Alveolar proteinosis has also been reported after exposure to busulfan
- Does not respond to therapeutic BAL

Cyclophosphamide

- Incidence of adverse pulmonary effects is 1%
- Pathogenesis not established - likely to be oxidant-mediated

- Metabolized →2 active agents - phosphoramide mustard & acrolein both of which reduce hepatic glutathione stores
- Chronic pneumonitis and/or fibrosis most common clinical manifestations

- Symptoms → 2 weeks to 13 years, without any clear dose relationship

- Synergistic toxicity in patients receiving radiation therapy / cytotoxic agents

Cancer 1985; 55:57–60

- Cyclophosphamide-induced PF present with B /L pleural thickening without clubbing & “Velcro” crackles

- Prognosis is generally poor → mortality rate approaching 50%

Am J Respir Crit Care Med 1996; 154:1851–1856

Methotrexate

- Incidence - 7% for high-dose / 2 to 3% with low-dose
- No clear dose relationship over a broad range (40 to 6,500 mg)
- Clinical manifestations:
  - hypersensitivity-type disease (most common)
  - chronic pneumonitis/fibrosis
  - COP
  - acute chest pain
  - Noncardiogenic pulmonary edema
  - acute pleurisy/pleural effusions
  - bronchospasm

- Hypersensitivity-type reactions→ 10 d to 4 mo
- Fever, cough, dyspnea, arthralgias & skin rash
- CXR - diffuse interstitial infiltrates
- HRCT scan - GGO
- Other - nodular infiltrates, hilar / mediastinal adenopathy & pleural effusion
- Blood eosinophilia in nearly 40%
- BAL fluid → predominance of lymphocytes (T- suppressor cells)

Eur Respir J 2000; 15:373–381

- Diagnosis requires 3 major criteria:
  - Histopathology - hypersensitivity pneumonitis
  - Radiographic evidence of interstitial and/or alveolar infiltrates
  - Negative blood cultures & sputum cultures

- 3 of 5 minor criteria:
  - Dyspnea of 8 weeks in duration
  - Nonproductive cough
  - RA O_2 saturation of ≤ 90%
  - Dlco of ≤ 70% of predicted
  - Leukocyte count of ≤ 15,000 cells/L

- Risk factors for toxicity include :
  - Symptoms within first 32 weeks of therapy
  - Multidrug regimens (synergy with cyclophosphamide)
  - Age > 50 yr / DM
  - Rheumatoid pleuro-pulmonary disease
  - Hypoalbuminemia

Ann Intern Med 1997; 127:356–364

- No affect of dose, frequency, smoking status, previous lung disease & route on adverse effect
- PFT – not helpful in identifying at risk pt on low dose
- Chronic fibrosis develops ~ 7% of hypersensitivity reactions
- 8% die of progressive respiratory failure

Mitomycin

- Incidence ~ 5% (3 to 39%)
- Radiographic / physiologic changes similar to bleomycin

- Most frequently after 3rd cycle
- Serial monitoring of Dlco to detect clinically occult disease unproven but generally recommended

- Prednisone rapidily resolve symptoms / interstitial infiltrate

- Rarely induce microangiopathic hemolytic anemia concurrently with NCPE & renal failure which has mortality rate of 90%

Retinoic Acid

- ATRA highly effective biological response modifier used to induces CR in acute promyelocytic leukemia
- Retinoic acid syndrome → ARDS-like seen in ~ 25% pt

- Sudden onset of fever, dyspnea, pleural / pericardial effusion, diffuse alveolar infiltrates & HRF
- Prednisolone (75 mg/d) reduces incidence ~ 8%

- Before steroid > 50 % patients required mechanical ventilation & mortality rate was 33%

Leukemia 1995; 9:774–778

Chemotherapeutic Agents/Newer Antineoplastic Drugs

- **Chlorambucil** → Tt of lymphoproliferative disorders has relatively rare toxcity – chronic pneumonitis / fibrosis

- **Cytosine arabinoside** → acute leukemia causes NCPE in 13 to 20% of patients
- Mortality rate 2 to 50% with reports of improve outcome with CS

- **Fludarabine** → cause chronic pneumonitis/fibrosis / hypersensitivity-type reaction which respond to CS

Chest 2002; 122:785– 790

- **Gemcitabine** →Mx of solid tumors can induce potentially fatal ARDS
- Toxicity ranges from 1 to 1.4% &includes
  - ARDS, NSIP, PF & PE

- **Taxanes** → induces bronchospasm & T1 hypersensitivity reaction in 30%
- HP, NSIP, PF ARDS & PE

- **Topoisomerase I inhibitors** (irinotecan / topotecan) → NSIP and bronchiolitis obliterans
- Synergy between irinotecan and paclitaxel or radiation↑ frequency of pulmonary toxicity from 1.8 → 13% or 56%, respectively

Chest 2008; 133:528–538

gefitinib and imatinib

- pulmonary toxicity in ~ 2% consisting of NSIP, HP, PF, COP, alveolar hemorrhage, ARDS, & PE

- GM-CSF & G-CSF can cause a HP when administered in conjunction with other cytotoxic agents

- G-CSF – induce ARDS in presence of cytotoxic drugs

Nonchemotherapy-Associated Pulmonary Toxicity

Antiinflammatory Drugs

- Aspirin-bronchospasm and noncardiogenic pulmonary edema

- Aspirin-induced asthma occurs in 1% of healthy individuals and in up to 20% of asthmatic individual

- Symptoms of AIA occur within minutes to hours after ingestion and may be associated with facial flushing, rhinorrhea, angioedema, and conjunctivitis

- **Penicillamine**: antiinflammatory, antifibrotic, & copper-chelating agent → RA, scleroderma, primary biliary cirrhosis, and Wilson disease

- Pulmonary toxicity include
  - interstitial pneumonitis/fibrosis
  - bronchiolitis obliterans ± organizing pneumonia
  - drug-induced SLE
  - alveolar hemorrhage due to a pulmonary-renal syndrome

- Incidence- < 1% with subacute onset of dyspnea, cough, & wheez
- CXR - hyperinflation in the absence of infiltrates
- PFT- ↑ lung volumes & airflow limitation without BDR
- Lung biopsy →bronchiolar constriction caused by mononuclear inflammation & fibrosis

- Mx →drug withdrawal, supportive therapy, & consideration of a trial of corticosteroids, azathioprine, or cyclophosphamide
- Prognosis →bronchiolitis obliterans is poor with 50% mortality

- **Etanercept, Infiximab & Adalimumab** → used to block effects of TNF- in autoimmune diseases

- Reactivation of tuberculosis / fungal infections

- Recommended : screening & treatment for latent tuberculosis before use of drug

- Etanercept / Infliximab → NSIP, PF, loosely formed granulomatous inflammation, PE, ↑ size of RA nodules & SLE-like reactions

Am J Med 2006; 119:639–646
Respir Med 2009; 103:661–669

Antimicrobial Drugs

- **Nitrofurantoin**
  - acute hypersensitivity-type reaction
  - chronic pneumonitis/fibrosis that mimics IPF

- Acute toxicity is a very rare (0.1%) seen with in 1 month of the first dose in 86% of patients

- Symptoms consist of dyspnea, cough, fever, chest pain, and a macular/papular skin rash

- Elevated ESR & peripheral blood eosinophilia

Eur J Respir Dis 1981; 62:180–189

- CXR
  - mixed alveolar/ interstitial infiltrative pattern
  - normal in 18% of patients
  - 1/3 have a small pleural effusion
- PFT - Restrictive pattern with reduced Dlco
- Prognosis → favorable with drug withdrawal and therapy with corticosteroids
- ARDS seen in few with overall mortality rate 1%

Cardiovascular Drugs

- **Amiodarone** → ventricular and SV arrhythmias refractory to other drugs
- Iodine - containing phospholipase inhibitor that causes lipid accumulation in nearly all tissues - lungs, skin, & liver

- Adverse pulmonary effects → 5 to 10% with high daily dose (400 mg/d) & prolonged duration (12 months)
- Large volume of distribution & long half-life of 30 to 60 days

- Lipid blockade → accumulation of undigested surfactant phospholipids in lung seen in virtually all patients

- Histological features
  - accumulation of foamy macrophages with characteristic lamellated inclusions in interstitium / alveolar spaces
  - hyperplasia of alveolar type II cells
  - widening of the alveolar septa with infiltration of lymphocytes, plasma cells, eosinophils, and neutrophils

- Pulmonary toxicity manifest as
  - interstitial pneumonitis/fibrosis, ARDS, COP,
  - mass lesions that can cavitate
  - EP, DAH and PE
- Uncommon reactions include HP, alveolar hypoventilation, and bronchospasm

- Risk factors
  - maintenance dose of 400 mg/d
  - age > 60 years
  - duration 6 to 12 months
  - angiography/acute lung injury
  - Cardio-thoracic surgery/ARDS

- Total cumulative dose or serum levels are not useful

- ↓in Dlco & ↑ gallium uptake are supportive but not reliable predictors of toxicity in absence of clinical / radiographic abnormalities

- Diagnosis is one of exclusion
- Chest CT scans → high-attenuation areas caused by the iodine
- KL-6 glycoprotein secreted by alveolar type II cells is useful serum marker → increased (> 500 U/mL) in ILD caused by IPF, radiation, amiodarone
- sensitivity and specificity of an increased serum KL-6 level is 94% and 96%, respectively

Am J Respir Crit Care Med 2002; 165:378– 381

- Mx→ withdrawal & new antiarrhythmic agent / implantation of an automatic cardioverter/defibrillator
- CS trial in symptomatic patients but efficacy not established
- Radiographic resolution in about 2 months & Tt to continue at least 6 months to reduce likelihood of relapse
- Recurrent can occur & if amiodarone is only effective agent
  - dose must be reduced to the minimum & CS to be added

Illicit Drugs

Causes wide array of pulmonary disorders

- Alveolar hypoventilation (hypercarbic respiratory failure)
- Aspiration
- Noncardiogenic pulmonary edema
- Barotrauma
- Endocarditis/septic emboli
- Foreign-body granulomatosis
- PIE
- COP
- Alveolar hemorrhage
- Bronchospasm
- Interstitial pneumonitis/fibrosis
- HIV associated infection.

- NCPE complication of **heroin, cocaine**, **methadone** & **Naloxone**

- Pathogenesis not clear but proposed
  - Altered alveolar/capillary permeability
  - Neurogenic pulmonary edema
  - Direct opiate cytotoxicity
  - Drug hypersensitivity
  - Hypoxemic alveolar injury

- Mx - supportive care including MV → needed in 40%
- Prognosis good with resolution of PE in 48 to 72 h

Radiation

- Thoracic irradiation causes dose-related reversible changes characterized by →dry cough & pathologic changes of bizarre type II cells, hyaline membranes, edema, & fibrosis

- Patients who receive therapy for lung or breast carcinoma, Hodgkin's disease or NHL, or total body irradiation before bone marrow or peripheral stem cell transplantation

- Expression of radiation injury to lung depends upon direction of radiation beam

- Induce changes in areas remote from radiation beam as suggested by
  - ↑ BAL lymphocytes or gallium uptake in both irradiated & non-irradiated lung
  - Organizing or eosinophilic pneumonia following breast radiation therapy may involve nonirradiated areas
  - Acute severe radiation pneumonitis and ARDS outside irradiated lung

- Concomitantly affect pleura, myocardium, heart valves, pericardium, pulmonary veins, mediastinum, lymphatic channels, & phrenic nerves

- The risk of radiation pneumonitis depends on
  - individual susceptibility of host
  - Delivered dose to lung
  - Daily / fractionation schedule
  - Treatment with chemotherapeutic agents or oxygen
- Other factors include older age and a low baseline lung function or PaO_2
- Recent pneumonectomy is a potential risk factor because
  - pulmonary reserve is compromised
  - remaining lung can be exposed to radiation as post-pneumonectomy hemithorax contracts

Ongoing smoking may have a protective effect

Toxicity Criteria for Pneumonitis

	Grade				
Scoring System	**1**	**2**	**3**	**4**	**5**
CTCAE	Asymptomatic; radiographic findings only	Symptomatic; not interfering with ADL	Symptomatic; interfering with ADL; O_2 indicated	Life-threatening ventilatory support indicated	Death
RTOG/EORTIC (LENT-SOMA)	Asymptomatic or mild symptoms (dry cough), with radiographic findings	Moderately symptomatic (severe cough fever)	Severely symptomatic	Severe respiratory insufficiency; continuous oxygen/assisted ventilation	Death
SWOG (33)	Asymptomatic or symptoms not requiring steroids with radiographic findings	Initiation of or increase in steroids required	O_2 required	Assisted ventilation necessary	Death

Notes: Abbreviations: *CTCAE = Common Terminology Criteria for Adverse Events; ADL = activities of daily living; RTOG = Radiation Therapy Oncology Group; EORTC = European Organization for the Research and Treatment of Cancer; LENT-SOMA = Late Effects on Normal Tissue-Subjective, Objective, Management and Analytic Scales; SWOG = Southwest Oncology Group.*

SOURCE: *Modified from Mehta V.:* Int J Radiat Oncol Biol. Phys *63:5–24, 2005, with permission.*

Fishman's Pulmonary Diseases and Disorders 4th Ed

- Patterns of radiation pneumonitis
  - Classic / sporadic radiation pneumonitis
- Approximately 10% of patients develop radiographic changes consistent with radiation pneumonitis
- Symptoms include a dry cough, moderate fever, and dyspnea
- On imaging, changes typically develop 1 to 2 months → discrete haze, ill-defined patchy nodules or an area of condensation
- Mild restrictive lung function can develop early in the course of radiation pneumonitis

Clin Chest Med 2004;25:167– 77.

- lung volumes normalize in 18 to 24 months
- lung biopsy is rarely needed to establish the diagnosis
- Histologic features
  - Interstitial edema, hemorrhage, and a fibrinous exudate in early stage
  - Distortion, fibrosis, and type 2 pneumocyte dysplasia in late stage

- Patients respond well to the administration of corticosteroids

- Late complications of chronic radiation pneumonitis
  - bronchiectasis in the fibrotic area
  - Pneumothorax
  - colonization by Aspergillus spp.
  - radiation-induced myocardial or valvular injury

Summary

- Different drugs can cause similar pulmonary syndromes and presentations
- Most common presentations are an abnormality on the chest radiograph and a symptom complex
- Early diagnosis is very important and requires the physician to be vigilant for problems in the appropriate clinical settings
- The diagnosis is usually one of exclusion
- Stopping the drug is sufficient therapy for most drug toxicities
- Corticosteroid administration may also be needed

THANKS