به نام خدا

فارماکوویژیلانس و عوارض ناخواسته داروها

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Drug-Induced Pulmonary Toxicity

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Introduction

- Drug-induced pulmonary toxicity is a diagnosis of exclusion
- >600 medications have been reported to cause drug-induced pulmonary toxicity
- Other disease processes must be ruled out
- These diseases include:
  - Respiratory infections
  - Occupational
  - Recreational
  - Environmental exposures
  - Specific respiratory disorders
  - Systemic diseases

Classification

- ADR can involve:
  1. The Pulmonary Parenchyma
  2. The Pleura
  3. The Airways
  4. The Pulmonary Vascular System
  5. The Mediastinum
  6. The Neuromuscular System
- These reactions can manifest acutely, subacutely, or chronically
- Illicit drugs are well-known to result in pulmonary toxicities

Signs & Symptoms

- Drug-induced lung diseases have no pathognomonic clinical, laboratory, physical, radiographic, or histologic findings
- Drug-induced lung disease is usually considered a diagnosis of exclusion

Criteria

- Correct identification of the drug, its dose, and its duration of administration
- Exclusion of other primary or secondary lung diseases
- Appropriate latent period (exposure to toxicity)
- Recurrence with rechallenge
- Singularity of drug
- Remission of symptoms with removal of the drug
- Characteristic pattern of reaction to a specific drug
- Quantification of drug levels that confirm abnormal levels (for overdoses)
- Degree of certainty of drug reaction (ie, causative, probable, or possible)

Diagnose

- We use clinical findings versus laboratory analyses in establishing the diagnosis of drug-induced pulmonary toxicity
- Chest radiographs are typically obtained
- High-resolution computed tomography (CT) scanning is more sensitive than chest radiography

Diagnosis

- What observed in drug-induced pulmonary toxicity are highly variable and depend on the type of adverse reaction
- Since most of the drug-induced pulmonary toxicities involve the parenchyma, interstitial infiltrates may be demonstrated on radiographs.
- Pleural fluid may be the only finding
- The radiograph may be normal or minimally abnormal if the airways or pulmonary vasculature is being affected

Aspirin-Exacerbated Respiratory Disease

Deffinition

- Aspirin-exacerbated respiratory disease refers to the combination of:
  1. Asthma
  2. Chronic rhinosinusitis (CRS) with nasal polyposis
  3. Reactions to aspirin and NSAIDs

Clinical Manifestation

- Nasal Congestion
- Bronchoconstriction
- Begin 20 min to 3 h after ingestion

Pulmonary Disease Induced By Cardiovascular Drugs

Amiodarone

Dose Dependent (>400 mg/day)

- Including interstitial pneumonitis (>2month)
- Organizing pneumonia
- Acute respiratory distress syndrome (ARDS)
- Diffuse alveolar hemorrhage (DAH)
- Pulmonary nodules
- Solitary masses
- Pleural effusion

Clinical Manifestation

- Insidious onset of nonproductive cough and/or dyspnea, which are present in 50-75% at presentation
- Fever is present in 33-50%
- Pleuritic Pain
- Weight Loss
- Malaise
- Bilateral inspiratory crackles, while clubbing is not seen

Lab Findings

- ↑ WBC count
- ↑ Serum LDH
- ↑ C-reactive protein
- ↑ ESR
- Eosinophilia and ANA are not typically seen
- Amiodarone levels are usually within the normal range
- PFT typically show a restrictive pattern
- Ground Glass Opacities

Beta Blockers

- Beta blockers can exacerbate diseases of the airways (COPD and asthma)
- pulmonary vasculature (eg, portopulmonary hypertension).
- pleural or pulmonary parenchymal diseases, such as drug-induced lupus and interstitial pneumonitis.

Asthma and COPD

- Beta-blocking medications are commonly used to treat hypertension, heart failure, and symptomatic coronary artery disease.
- However, beta-blocking medications that act on beta2 receptors can also cause bronchoconstriction.
- nonselective beta1/beta2 blockers (eg, propranolol) are more likely to cause bronchoconstriction in susceptible individuals
- In contrast, selective beta1-blockers (eg,atenolol, metoprolol) have a 20-fold greater affinity for beta1 adrenergic receptors than beta2 adrenergic receptors and, therefore, are less likely to induce bronchoconstriction.

Hydralazine

- Drug-induced lupus (pleural and pericardial effusions)
- Antineutrophil cytoplasmic antibody positive-pulmonary vasculitis
- Diffuse alveolar hemorrhage

Minoxidil

- Fluid retention is a potential adverse effect of the drug.
- Minoxidil has been associated with the development of pericardial and pleural effusions, which may be exudative

Nitrates

- Overdoses of nitrate medications, such as nitroglycerin or nitroprusside, can cause methemoglobinemia.
- The clinical presentation may include dyspnea, respiratory depression, cyanosis, lethargy, altered consciousness, hypotension, and seizures
- Measurement of oxygen saturation by a pulse oximeter may be inaccurate for assessing oxygen saturation as severe methemoglobinemia causes the SpO_2 to trend towards 85 percent and thus may either overestimate or underestimate the true arterial oxygen saturation (SaO_2) as measured by arterial blood gas analysis

Pulmonary Toxicity Associated With Systemic Antineoplastic Therapy

Introduction

- Adverse drug reactions (ADRs) due to antineoplastic agents are a common form of iatrogenic injury, and the lungs are a frequent target
- Some estimate that 10-20% of all patients treated with an antineoplastic agent have some form of lung toxicity (lungs receiving the entire blood supply)

Pathogenesis

- Direct injury to pneumocytes or the alveolar capillary endothelium with the subsequent release of cytokines and recruitment of inflammatory cells.
- The systemic release of cytokines (eg, by Gemcitabine) may result in endothelial dysfunction, capillary leak syndrome, and noncardiogenic pulmonary edema.

Pathogenesis

- Cell-mediated lung injury due to activation of lymphocytes and alveolar macrophages
- Oxidative injury from free oxygen radicals (eg, Bleomycin-related lung injury)
- Epidermal growth factor receptors (EGFR) are expressed on type II pneumocytes, and are involved in alveolar wall repair; agents targeting the EGFR may impair alveolar repair mechanisms.

Pathogenesis

- Radiation recall pneumonitis is mediated by the presence of subclinical cumulative parenchymal radiation-induced injury that becomes apparent when another pulmonary insult (ie, cytotoxic chemotherapy) is encountered at a later date.

Symptoms

- Symptoms are nonspecific & include:
  - Cough
  - Dyspnea
  - Low-grade fever
  - Hypoxemia
  - Weight loss, may be present
- Chills and sputum production are rarely reported

Signs

- Lung auscultation may reveal bibasilar crackles, but is often normal
- Wheezing is rare, but when present, suggests a hypersensitivity mechanism with a component of bronchoconstriction
- A morbilliform rash would provide evidence of hypersensitivity to a drug,
- Drug rash with eosinophilia and systemic symptoms (DRESS)

Timing & Pinpoint A Specific Agent

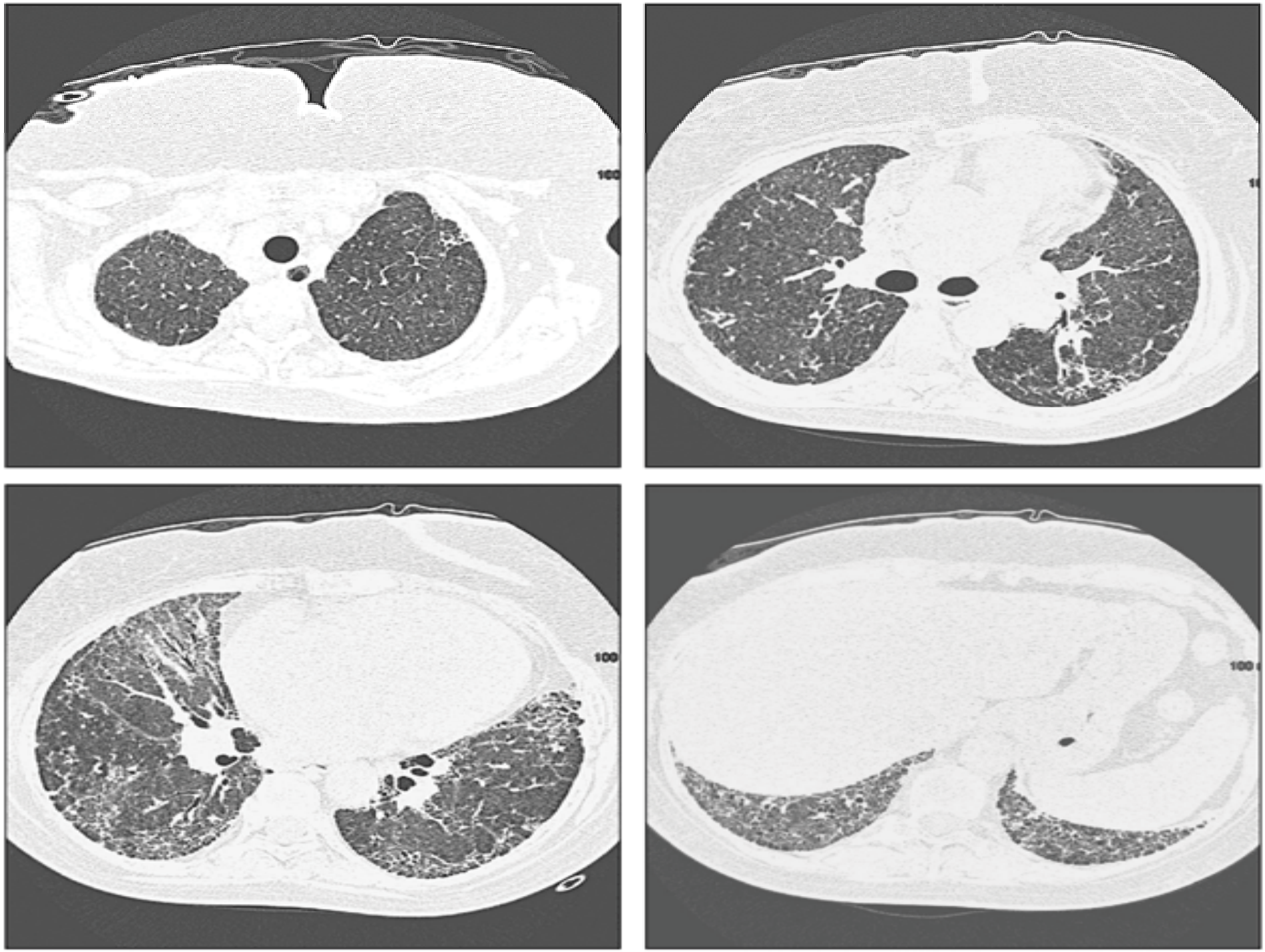
- Except delayed fibrosis seen with nitrosoureas and Bleomycin
- Typically lung toxicity occurs within weeks to a few months after initiation of therapy
- As most protocols consist of multiple drugs, it may be difficult to pinpoint the specific agent that is responsible for the lung toxicity
- Respiratory manifestations are almost never specific enough to incriminate one agent over another

Evaluation

- Pulmonary function testing (PFT)
  1. First: ↓DLCO
  2. Advanced Case: Restrictive PFT pattern
- Imaging
- Bronchoscopy & bronchoalveolar lavage

↓DLCO

- Significant reductions in DLCO could seen in:
  - Bleomycin
  - Gemcitabine
  - Paclitaxel
  - Platinum
  - Cyclophosphamide
  - Doxorubicin
- Small changes do not correlate with symptoms or operability



Imaging

- The most common abnormalities on high resolution computed tomography (HRCT) are Ground Glass Opacities
- Chest imaging of radiation recall pneumonitis shows a unique pattern of pulmonary opacities in exactly the same distribution as the previous radiation therapy portal.
- Agents suspected for:

Carmustine
Doxorubicin
Etoposide
Gefitinib
Gemcitabine
Paclitaxel
Trastuzumab

Bronchoscopy & bronchoalveolar lavage

- There are no specific findings for drug-induced lung toxicity on bronchoscopy or bronchoalveolar lavage (BAL).
- BAL fluid cell counts are usually elevated; lymphocytosis, neutrophilia, or rarely, eosinophilia may be seen
- The main role of bronchoscopy is to exclude infection, or recurrent malignancy

Diagnosis

- No specific tests establish the diagnosis, other than rechallenge with the implicated agent after a period of discontinuation.

Differential Diagnosis

- Infections
- Cardiogenic and non-cardiogenic pulmonary edema (Doxorubicin, Docetaxel)
- Direct involvement of the lungs by the neoplastic process
- Pulmonary hemorrhage (Bevacizumab & Sorafenib)

Treatment

1. Drug discontinuation
2. Glucocorticoids
3. Supportive Care

Drug Discontinuation

- No specific treatment has proven effective besides discontinuation of the suspected offending agent
- An exception to this rule is the differentiation syndrome seen in patients with acute promyelocytic leukemia who are treated with a differentiating agent

Glucocrticoids

- severe respiratory compromise is often treated with prednisone 40-60 mg daily; intravenous glucocorticoids (eg, methylprednisolone with doses up to 1 g daily for three days) have been be used in patients who have impending respiratory failure or require mechanical ventilation

Supportive Care

- Supportive care may include
- Supplemental oxygen
- Bronchodilating medication (eg, beta agonists) if wheezing, airflow obstruction on PFT
- mechanical ventilation (if indicated)
- Except Bleomycin (only if O2 sat<89%)

Rechallenge

- The decision to reintroduce the same drug in a patient who has recovered from drug-induced pulmonary toxicity must be made on a case by case basis
  1. Individual agent
  2. The severity of the reaction
  3. The availability of alternative therapies
- When the diagnosis is reasonable, we generally do not reintroduce the agent.
- Successful rechallenge has been reported with the differentiating agents (ATRA, or arsenic trioxide), dasatinib, and temsirolimus or everolimus

Pulmonary ADRs

- Interstitial pneumonitis (bortezomib, anthracyclines, fludarabine, gemcitabine, ifosfamide, irinotecan, oxaliplatin, thalidomide and lenalidomide, vinca alkaloids)
- Organizing pneumonia (doxorubicin, oxaliplatin)
- Diffuse alveolar damage (gemcitabine, oxaliplatin, etoposide)
- Opportunistic infections (bortezomib, fludarabine)
- Noncardiogenic pulmonary edema (cytarabine, gemcitabine, vinblastine)
- Radiation recall pneumonitis (doxorubicin, paclitaxel, gemcitabine)
- Eosinophilic pneumonia (gemcitabine, oxaliplatin, procarbazine)
- Alveolar hemorrhage (gemcitabine)
- Nonthromboembolic pulmonary hypertension (thalidomide)
- Thromboembolic disease, which may affect the lungs (thalidomide and lenalidomide)

Thanks For Your Attention