Noninfectious Inflammatory Lung Diseases

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Relevant Disclosures and Resolution

Under Accreditation Council for Continuing Medical Education guidelines disclosure must be made regarding relevant financial relationships with commercial interests within the last 12 months.

Jad Kebbe

I have no relevant financial relationship or affiliation with commercial interests to disclose.
Learning Objectives

Upon completion of this session, participants will improve their competence and performance by being able to:

1. Appraise the various processes of lung inflammation
2. Differentiate between pathways and etiologies
3. Review examples from different systems
4. Discuss latest data on vaping-related illnesses
Pulmonary physiology

• Lungs are complex and fascinating
• Primary function: gas exchange
• They are essential to living: you can withhold food or water for a long time, but not breathing!
• Intricate balance and symbiotic relation between air, tissue and blood
• Pulmonary circulation is a mixture of high and low blood flows
• There is a constant interaction between heart and lungs
Airway anatomy and physiology
Normal function of pulmonary cells
What in the lungs can become inflamed?

- Airways:
  - Epithelium cells can participate in local cytokine networks
  - They are themselves targets for numerous cytokines
- Glands
- Smooth muscle
- Cartilage
- Interstitial space
- Lymph nodes
- Vessels
- Pleura

Airway inflammation

- Examples of diseases:
  - Asthma
  - Chronic bronchitis
  - Bronchiectasis
  - Cystic fibrosis

- Asthma & chronic bronchitis affect 25 million persons in the USA

- Inflammation of the conducting airways is a feature of these conditions, characterized by airway obstruction and excessive airway secretions
Mechanisms of airway inflammation

• Several mechanisms of inflammation
  • Chemokines:
    • IL-8 mediates neutrophil chemotaxis in airway disorders
    • IL-8 induces eosinophil and T-lymphocyte chemotaxis, to modulate basophil histamine release
  • Cytokines
  • Growth factors
  • Inflammatory mediators
  • Lipid mediators

• Other mechanisms perpetuate the inflammatory process:
  • Neurogenic inflammation
  • Perpetuation of the acute inflammatory response
  • Cycles of airway epithelial cell-mediated & inflammatory cell-mediated recruitment and activation of inflammatory cells
Inflammatory mechanisms and pathobiologic features leading to severe asthma

Inflammatory mechanisms associated with granulocytic inflammation

Type 2 inflammation
- Allergens
  - CRTH2
  - GATA3
  - IL-33
  - IL-4, IL-5, and IL-13
  - IL-4

Non-type 2 inflammation
- Inflammasomes, pollutants, microbes, and viruses
  - CRTH2
  - IL-33
  - IL-6
  - IL-8
  - TNF-α
  - IFN-γ
  - Leukotriene B4

Hyperresponsiveness, remodelling, mucus production, and smooth-muscle constriction and hypertrophy
Pulmonary vascular inflammation

• Vascular circulation in the lungs is unique:
  • Pulmonary circulation: carries deoxygenated blood from the right ventricle to the lungs, and returns oxygenated blood to the left atrium
  • Bronchial circulation: supplies oxygenated blood to pulmonary tissue of larger airways

• Most common pulmonary vasculitides:
  • Granulomatosis with polyangiitis (GPA)
  • Microscopic polyangiitis

• Less common pulmonary vasculitides:
  • Goodpasture
  • Eosinophilic granulomatosis with polyangiitis (previously: Churg Strauss)
Granulomatosis with Polyangiitis

• GPA can affect arteries, arterioles, capillaries, venules, and veins

• Histopathology:
  • Transmural vascular infiltration with inflammatory cells
    • Neutrophils
    • Lymphocytes
    • Multinucleated giant cells
    • Eosinophils (not abundant)
  • Associated with granulomatous inflammation in the surrounding tissue

• Unique features of granulomatous inflammation: palisading histiocytes oriented with their long axis perpendicular to the necrotic center

• May be ANCA positive (c-ANCA; antiproteinase-3)
Microscopic polyangiitis

• Unlike GPA, there are no necrotizing granulomas
• Pulmonary presentations can be similar with capillaritis in diffuse alveolar hemorrhage
• Other manifestations:
  • Nodules
  • Interstitial lung diseases
  • Bronchial inflammation and stenosis
• May be ANCA positive (p-ANCA; antimyeloperoxidase)
• Both diseases require immunosuppression
Closer up view: Neutrophils in the vessel wall
Sarcoidosis

- Multisystem inflammatory disorder
- May affect airways, interstitium, and lymph nodes
- Mechanism: lymphocytic inflammation that causes non-caseating granulomas
- Important to rule out infections
- May affect several organs:
  - Eyes
  - Brain
  - Kidneys
  - Liver
  - Skin
Pneumonitis

• Can be idiopathic or secondary

• Causes of pneumonitis:
  • Connective tissue diseases e.g. systemic sclerosis, rheumatoid arthritis
  • Inhalational injury e.g. toxic fumes, silica
  • Organic antigens e.g. bird feathers, mushroom spores, mold
  • Respiratory distress
  • Surfactant deficiency
  • Drugs e.g. checkpoint inhibitors, monoclonal antibodies, platinum-based chemotherapy
Mechanisms of pneumonitis

- Lymphocyte mediated (CD8+ T cells): hypersensitivity pneumonitis
- Eosinophil mediated: acute and chronic eosinophilic pneumoniae
- Chemical: aspiration
- Radiation
- Collagen deposition and fibroblast proliferation (osteopontin, surfactant protein D, matrix metalloproteinases, TGF-β): fibrosis
- Organic antigens: avian antigens, mold, mushroom
- Inorganic antigens: coal, silica, asbestos, cobalt
Health department confirms first case of vaping-associated lung injury in Oklahoma

The latest weekly tally includes 275 more reports of patients sickened, in 46 states. There are now 12 deaths linked to vaping.
A new culprit in pneumonitis: vaping!

- E-cigarettes are battery-operated devices that heat a liquid and deliver an aerosolized product to the user: electronic nicotine delivery system
- 2006 was the year marking the entry of vaping to the US market
- In 2019, there is an ongoing surge in reported cases of acute lung illnesses, including death
- 84% of patients reported having used tetrahydrocannabinol products in e-cigarette devices
- As of September 2019, the CDC has confirmed more than 350 cases in 36 states, which it declared as an “epidemic of severe lung disease”
Vaping: prevalence and popularity

• 2013: 8.5% of adults report ever having used an e-cigarette/vaping
• 2016: the percentage had increased to 15%
• 2018:

2% of high school students reported current use of e-cigarettes.
5% of middle school students reported current e-cigarette use.

(esp the “Juul” branded vaping devices).

DELNEVO ET AL. PATTERNS OF ELECTRONIC CIGARETTE USE AMONG ADULTS IN THE UNITED STATES. NICOTINE TOB RES. 2016;18(5):715
Juul are cheap, easy to use, and popular

“Starter kit” including device, charging dock, 4 flavor pods runs $29.99.

Private company based out of San Francisco, 2018 revenue of $2 billion.

“Juuling” is a term significant with vaping use the Juul device.
Vaping nomenclature

- **Dripping** refers to dripping a few drops directly onto heating element
- **Dabbing** refers to using a device to inhale vapors from “dabs” which are supposed to be concentrated THC in an oil/wax preparation.
  - **Oil**: oily base extract of marijuana referred as Butane Hash Oil or Honey Oil
  - **Shatter**: glassy solid concentrate of oil that has been heated in a vacuum oven
  - **Budder**: solvent extraction of dried marijuana with an oil product that is “whipped”
  - **Wax**: yellowish cured marijuana that feels waxy
Possible culprits

- Flavorants
  - e.g. diacetyl, a chemical linked to severe lung disease
- Volatile organic compounds
- Heavy metals
  - Nickel
  - Tin
  - Lead

- No one specific liquid or device has been identified as the causative agent
- Illnesses have been reported with the use of nicotine, THC, and CBD
Acute presentation of vaping-related illness

- Nearly 100% of patients have respiratory symptoms
- All patients have bilateral pulmonary infiltrates
- 94% of patients hospitalized
- 32% of patients intubated
- 84% of patients reported using Tetrahydrocannabinol
- Median age: 19 years
- %males: 83%
Acute presentation of vaping-related illness
Cytopathology

- A high level of lipid-laden macrophages with oil red O stain
- Only few biopsies performed
- Identified pathologies and types of pneumonitis:
  - Mild and nonspecific inflammation
  - Acute diffuse alveolar damage and foamy macrophages
  - Interstitial and peribronchiolar granulomatous pneumonitis
  - Chemical pneumonitis
  - Acute eosinophilic pneumonia
  - Acute and subacute hypersensitivity pneumonitis
  - Lipoid pneumonia
  - Metal fume fever
  - Polymer fume fever
The CDC recommends that clinicians report cases of vaping-related illnesses to their state or local health department, as well as the FDA at https://www.safetyreporting.hhs.gov/SRP2/en/Home.aspx?sid=cc7873df-0590-49ec-9d71-ecbf742d34e3 and collect the following information:

- Type of device(s) used (e.g. bottles, cartridges or pods)
- Specific type(s) of liquid used (e.g. nicotine, THC products, flavored fluids)
- Were devices, liquids, refill pods and/or cartridges shared with other people?
- Were old cartridges or pods reused with other homemade or commercial products?
- Were devices used to inhale drugs that were concentrated by heating prior to vaping (i.e., “dabbing”)?
- Details of vaping behavior (e.g. cloud volume, frequency of puffs, ‘zero’ or ‘stealth’ vaping, valsalva at end inhalation).
Organizing Pneumonia

- Can occur without discernible cause (cryptogenic) or associated with connective tissue disorders, drugs, or following an injury
- Usually presents like a typical bacterial pneumonia
  - Fever, cough, malaise, dyspnea
- Patient improves slightly after initiation of antibiotics
- However, condition recurs with similar presentation
- Might be difficult to diagnose
- High lymphocyte count on bronchoscopic lavage
- Chest imaging: peripheral subpleural consolidations with varying locations during different presentations
- Treatment: corticosteroids
Case Study

• 60 y o F with RA presents with mild dyspnea and right pleural effusion
• Pleural pressure turns negative during thora as she develops chest pain
• Fluid analysis:
  • pH: 7.18
  • Glu <10
  • Protein: 4.9
  • LDH: 1681
  • Triglycerides: 21
  • Cholesterol: 388
Pleural Effusion

A very common entity
- 1-1.5 million new cases/y in USA
- 80,000-160,000 new cases of malignant effusions/y

Characteristics of pleural space:
- Pressure: -3 to -5 cm H2O
- Volume: 0.26 mL/kg
- Produced and absorbed by parietal surface
- Parietal lymphatic vessels are responsible for resorption
- Resorption rate can increase 20 times in response to increased fluid formation

Non-Malignant Effusions

Broad variety and many causes

Often poorly understood

Hard to classify

Main divisions:
- Transudate vs exudate
- Unilateral vs bilateral
- Infectious vs non-infectious
- Subclinical vs symptomatic

Exudative effusions

- Infectious: bacterial, viral, tuberculosis-related, fungal, parasitic
- Neoplastic: metastatic disease (e.g., lung cancer, breast cancer, lymphoma, myeloma, ovarian cancer, pancreatic cancer, cholangiocarcinoma), mesothelioma, primary body-cavity lymphoma
- Paramalignant effusions: reactive pleuritis due to underlying lung cancer, airway obstruction or atelectasis, radiation-induced pleuritis
- Reactive: reactive pleuritis due to underlying pneumonia (i.e., parapneumonic)
- Embolic disease: pulmonary embolism
- Abdominal disease: pancreatitis, cholecystitis, hepatic or splenic abscess, esophageal perforation after esophageal varix sclerotherapy
- Cardiac or pericardial injury, including myocardial infarction (after coronary-artery bypass, cardiac surgery, or cardiac ablation procedures), pulmonary-vein stenosis
- Gynecologic: ovarian hyperstimulation, Meigs’ syndrome, endometriosis, postpartum complications
- Collagen vascular disease: rheumatoid arthritis, systemic lupus erythematosus, Sjögren’s syndrome, familial Mediterranean fever, eosinophilic granulomatosis, granulomatosis with polyangiitis
- Medications: nitrofurantoin, dantrolene, methysrgide, dasatinib, amiodarone, interleukin-2, procarbazone, methotrexate, clozapine, phenytoin, β-blockers, ergot drugs
- Hemothorax
- Chylothorax (most commonly seen after trauma or in patients with lymphoma)
- Sarcomiosis
- Lymphoplasmacytic lymphoma
- Cholesterol effusions (commonly seen in tuberculosis, rheumatoid effusions, and any other chronic pleural effusion)
- Miscellaneous: benign asbestos pleural effusion, yellow nail syndrome, uremia, drowning, amyloidosis, electrical burns, iatrogenic effusion, capillary leak syndromes, extramedullary hematoopoiesis
Non-Malignant Effusions

Management predominantly focuses on relief of symptoms
Mortality often depends on the underlying cause
They cause substantial morbidity
Adequate treatment relies on identifying an underlying etiology

<table>
<thead>
<tr>
<th>Transudative effusions</th>
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<tbody>
<tr>
<td>Congestive heart failure</td>
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<tr>
<td>Cirrhosis</td>
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<td>Nephrotic syndrome</td>
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<tr>
<td>Glomerulonephritis</td>
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<tr>
<td>Peritoneal dialysis</td>
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<tr>
<td>Hypoalbuminemia (typical serum albumin, &lt;1.5 mg/dl)</td>
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<td>Atelectasis</td>
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<td>Superior vena cava obstruction</td>
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<td>Trapped lung</td>
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<td>Sarcoidosis</td>
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<tr>
<td>Peritoneal dialysis</td>
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<tr>
<td>Myxedema</td>
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<tr>
<td>Cerebrospinal fluid leak or ventriculopleural shunt</td>
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<tr>
<td>Urinothorax</td>
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<td>Pulmonary arterial hypertension</td>
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<td>Pulmonary embolism</td>
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<tr>
<td>Pericardial disease</td>
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<td>Extravascular migration of central venous catheter</td>
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Common Causes

More than 50 etiologies

**Transudative:** cardiac (CHF, constriction), renal (nephrotic Sd), or hepatic (cirrhosis, hypoalbuminemia) origin

**Exudative:** excess inflammation (malignancy, infection, autoimmune, pancreatitis, PE, post-CABG, esophageal rupture...)

The most common cause of a transudate (and effusions as a whole) is **heart failure**

Up to 57% of patients with pneumonia develop an effusion
Conclusion and Clinical Pearls

• Inflammation can affect any lung structure

• Certain pulmonary inflammatory conditions are associated with systemic manifestations

• Beware of vaping associated pulmonary inflammation and consult a specialist early
New commandment

Thou shalt not vape!
Thank you!