Eosinophilia Associated Lung Diseases

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Disclosure

- Basic and Clinical Research
  - NHLBI (AsthmaNet, SARP, SPIROMICS)
  - ALA (ACRC)
- Book Chapters
  - UpToDate
  - Merck Manuals
- Pharmaceutical Trials
  - Actellon, Amgen, Astra-Zeneca, Boehringer-Ingelheim, Centocor, Cephalon, Genentech, GlaxoSmithKline, Forest, Medimmune, Sanofi-aventis
- Advisory Boards
  - Array Biopharma, AstraZeneca, Astoril, Arinact AB, Boehringer-Ingelheim, Experts in Asthma, Gilead, GlaxoSmithKline, Merck, Novartis, Ovo Pharmaceutical, Pfizer, PPD Development, Quintiles, Sunovion, Saatchi & Saatchi, Targacept, TEVA, Theron
- Speakers' Bureaus
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  - Case Reports in Medicine
  - US Resp Disease
  - J Pulm Resp Medicine
  - Clin Exp Med Sciences
  - JACI: In Practice

Eosinophilia Associated Lung Diseases: Learning Objectives

In a Clinical Approach:
- Review Important Eosinophil-Associated Lung Diseases
- Discuss the Differential Diagnosis and Distinguishing Features of These Disorders and Treatment Approaches
Eosinophilia and Eosinophilic Lung Disease

- **Peripheral Eosinophilia**
  - > 400 – 500 Eosinophils/µl
- **Pulmonary Eosinophilia**
  - Tissue Eosinophilia
  - BAL Fluid > 5% (normal <1%)
- **Mechanisms**
  - cytokine-mediated (mainly IL-5) increased differentiation and survival of eosinophils (extrinsic eosinophilic disorders)
  - Mutation-mediated clonal expansion of eosinophils (intrinsic eosinophilic disorders).


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**Case 1 - Presentation**

46 Yr Women Transferred from Central PA Hosp – “Severe Asthma”
- 2 yr cough, wheeze, fatigue
- HBP, depression, migraines
- OCS, (ICS), Salm, Terbut. (PPI, Cipro, Estrogen)
- Hairdresser
- Hunter (Deer, Bear), Fishing
- Exam – Cushingoid, Clear Lungs (PEF always low)
- WBC 14K (86P, 1E)
- ABG 7.42/42/70

- Spirometry
  - FEV1/FVC 79% (nl)
  - FEV1 70% pred
  - FVC 72% pred
- TLC 76% pred (Restrict)
- DLCO 50% pred
- CXR, CT chest (nl with min atelectasis)
- ECHO - WNL

Methacholine - WNL
Withdrawn Medication
Resp Failure – ICU, OLbx
Eosinophilia Associated Lung Disease and Asthma Mimic – Eosinophilic Interstitial Pneumonitis

Eosinophilic Lung Diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Prevalence of disease</th>
<th>Degree of peripheral blood eosinophilia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>Common</td>
<td>Mild (up to moderate in SIDs and with nasal polyposis)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>Common</td>
<td>Mild</td>
</tr>
<tr>
<td>Eosinophilic bronchitis</td>
<td>Common (10% of chronic cough)</td>
<td>Mild</td>
</tr>
</tbody>
</table>

Eosinophilic Lung Diseases: Asthma
Key Elements of Asthma

• Reversible (partial) Airflow Obstruction
• Bronchial Hyperresponsiveness
• Intermittent Symptoms
• PFTs –
  – No Restriction (NI, Elevated TLC)
  – Diffusing Capacity (DLCO) NI (Elevated)
• Imaging – (CXT, CT) Usually Normal
Sputum Eosinophils in Steroid-Treated vs Steroid-Untreated Subjects with Asthma

McGrath, et al. AJRCCM 2012;185:612–619

Characteristics of AECOPD Patients

Obstructive Lung Diseases Differentiating Asthma from COPD

• COPD
  – Emphysema (Decreased D,CO)
  – Chronic Bronchitis (History - Cough & Spit)

• Asthma
  – Normal Diffusing Capacity (Could be increased with Exacerbation and Hyperinflation)
  – Chronic Sputum Production Less Common
Syndromes of Disordered Airway Function

Case 2 - Recurrent Post-Partum Pulmonary Eosinophilia

23 year old woman developed idiopathic eosinophilic pneumonia which was successfully treated with corticosteroids. She subsequently developed two identical relapses in the post-partum period.

Principal Forms of Pulmonary Eosinophilia (clinical-radiological presentation)

1) Simple pulmonary eosinophilia (Löffler’s)
2) Chronic eosinophilic pneumonia (CEP)
3) Acute eosinophilic pneumonia (AEP)

Not all cases have Peripheral Eosinophilia
Peripheral Infiltrates on Imaging
BAL Eosinophilia Characteristic
Differentiating Factors
• Chronicity - < 30 Days (Löffler’s) + Steroids vs CEP
• Acute Respiratory Failure (AEP)
**Eosinophilic Lung Diseases**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Prevalence of disease</th>
<th>Degree of peripheral blood eosinophilia*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paroxysmal airway colonization</td>
<td>Regarded as unusual but probably common in patients with more severe disease</td>
<td>Mild to moderate</td>
</tr>
<tr>
<td>Eosinophilic pneumonia (EP)</td>
<td>Unusual</td>
<td>Moderate to severe</td>
</tr>
</tbody>
</table>

**Allergic Bronchopulmonary Aspergillosis (ABPA)**

**Clinical Features of ABPA**
- Asthma-Like Syndrome
- May Have Sputum (“black plugs”)
- Pulmonary Infiltrates (may be “fleeting” and recurring in same areas)
- Airway Obstruction which can Progress to Restriction
- Corticosteroid Responsive

**Diagnosing ABPA**
- Asthma with central bronchiectasis (late and “pathopneumonic”) or pulmonary infiltrates
- Total IgE levels greater than 1,000 ng/ml
- Positive skin test reactivity to *Aspergillus sp.*
- IgE or IgG against *Aspergillus sp.* in the blood
**Case 3 – Presentation**

*Wechsler. JAMA 1998; 279:455-457*

Healthy Woman, Sinusitis and Asthma at 40 yr
- ICS, theo, β-Ag, frequent OCS
- Zafirlukast – Improved over 2 mo; D/C OCS
- 2 wk – Rash, Fever, Diarrhea, Dyspnea
- Tachycardia, Wheezes
- Unilateral Foot Drop

- WBC 26K, 37% Eos
- CXR – Patchy Infiltrates
- ECHO – Global Hypokinesis, EF 35-40%
- Skin Bx – lymphocytic and eos perivascular infiltrates
- Lung Bx – Necrotizing, granulomatous vasculitis
- Treatment – Corticosteroids and Cyclophosphamide

Churg-Strauss: LTRA and Systemic Steroid Discontinuation

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**Churg-Strauss Syndrome**


1) **Allergic phase:** presence of asthma or rhinitis
2) **Eosinophilic phase:** presence of severe persistent peripheral eosinophilia (eosinophil count greater than 1,500 cells/mm³) for more than 6 months
3) **Vasculitic phase:** presence of systemic manifestations and small vessel vasculitis, represented by the involvement of two or more extrapulmonary organs.

*However, it is important to remember that the three phases can be dissociated. Asthma is present in 100% of cases.*

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**Xolair® (Omalizumab) – PI July 2008**

Eosinophilic Conditions:
In rare cases, patients with asthma on therapy with Xolair may present with serious systemic eosinophilia sometimes presenting with clinical features of vasculitis consistent with [Churg-Strauss syndrome](#), a condition which is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction of oral corticosteroid therapy. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in patients. A causal association between Xolair and these underlying conditions has not been established.
Principal Forms of Pulmonary Eosinophilia (clinical-radiological presentation)

4) Allergic bronchopulmonary aspergillosis
5) Pulmonary eosinophilia associated with a systemic disease:
   • Churg-Strauss syndrome
   • Hypereosinophilic syndrome

Asthma Plus Disorders

• Churg-Strauss Syndrome – Vasculitis, GI involvement, ?Medications
• Allergic Bronchopulmonary Aspergillosis – Infiltrates, Obstruction and Restriction, Elevated IgE
• Occupational Asthma (vs RAD – Reactive Airways Dysfunction) – History, PFTs
• Anaphylaxis – Multisystem, Serum Tryptase

Eosinophilic Lung Diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Prevalence of disease</th>
<th>Degree of peripheral blood eosinophilia</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSS</td>
<td>Rare</td>
<td>Severe</td>
</tr>
<tr>
<td>Idiopathic pulmonary fibrosis (IPF)</td>
<td>Unusual</td>
<td>Mild</td>
</tr>
<tr>
<td>Lung carcinoma</td>
<td>Common</td>
<td>Mild to severe</td>
</tr>
<tr>
<td>Infection with helminthic parasite</td>
<td>Common in countries where parasite infection is endemic</td>
<td>Severe</td>
</tr>
</tbody>
</table>

TABLE II: Eosinophilic lung diseases
Etiology of Pulmonary Eosinophilia

1) Primary or idiopathic
2) Secondary
   a) Known cause
      • Drugs
      • Parasites
      • Toxic products/irradiation
      • Fungal and mycobacterial infection

Drugs Associated with Eosinophilia

<table>
<thead>
<tr>
<th>Drug group</th>
<th>Drug examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aromatic anticonvulsants</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td></td>
<td>Phenytoin</td>
</tr>
<tr>
<td></td>
<td>Phenobarbital</td>
</tr>
<tr>
<td>Nonaromatic anticonvulsants</td>
<td>Lamotrigine</td>
</tr>
<tr>
<td></td>
<td>Valproic acid</td>
</tr>
<tr>
<td></td>
<td>Gabapentin</td>
</tr>
<tr>
<td></td>
<td>Benzodiazepines</td>
</tr>
<tr>
<td>Anticancer drugs</td>
<td>Allopurinol</td>
</tr>
<tr>
<td></td>
<td>Methotrexate</td>
</tr>
<tr>
<td></td>
<td>Rituximab</td>
</tr>
<tr>
<td></td>
<td>Haploidentical</td>
</tr>
<tr>
<td></td>
<td>Bortezomib</td>
</tr>
<tr>
<td></td>
<td>Abacavir</td>
</tr>
<tr>
<td>Sulfur drugs</td>
<td>Dapsone</td>
</tr>
<tr>
<td>Nonsteroidal anti-inflammatory</td>
<td>Sulfasalazine</td>
</tr>
<tr>
<td>drugs</td>
<td>Diclofenac</td>
</tr>
<tr>
<td>Antihypertensive drugs</td>
<td>Captopril</td>
</tr>
<tr>
<td>Antidiabetics</td>
<td>Diltiazem</td>
</tr>
<tr>
<td></td>
<td>Sorbitol</td>
</tr>
</tbody>
</table>

Parasites Causing Eosinophilia

<table>
<thead>
<tr>
<th>Phylum</th>
<th>Species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cestode</td>
<td>Mesocestoides corti*</td>
</tr>
<tr>
<td>Nematode</td>
<td>Hymenolepis diminuta</td>
</tr>
<tr>
<td></td>
<td>Anisakis species</td>
</tr>
<tr>
<td></td>
<td>Ascaris lumbricoides</td>
</tr>
<tr>
<td></td>
<td>Ancylostoma species</td>
</tr>
<tr>
<td></td>
<td>Bagnoi nasci species</td>
</tr>
<tr>
<td></td>
<td>Brugia species*</td>
</tr>
<tr>
<td></td>
<td>Enterobius vermicularis</td>
</tr>
<tr>
<td></td>
<td>Heteroascaris polygyrus</td>
</tr>
<tr>
<td></td>
<td>Litomosoides species*</td>
</tr>
<tr>
<td></td>
<td>Nippostrongylus species*</td>
</tr>
<tr>
<td></td>
<td>Onchocerca species*</td>
</tr>
<tr>
<td></td>
<td>Strongyloides species*</td>
</tr>
<tr>
<td></td>
<td>Toxocara species</td>
</tr>
<tr>
<td></td>
<td>Trichinella species*</td>
</tr>
<tr>
<td></td>
<td>Trichuris species</td>
</tr>
<tr>
<td></td>
<td>Wucheria bancrofti</td>
</tr>
<tr>
<td>Trematode</td>
<td>Fasciolus species</td>
</tr>
<tr>
<td></td>
<td>Schistosoma species*</td>
</tr>
</tbody>
</table>
Etiology of Pulmonary Eosinophilia

b) Diseases that can lead to pulmonary eosinophilia
- **Diffuse lung diseases**: cryptogenic organizing pneumonia; hypersensitivity pneumonia; idiopathic pulmonary fibrosis; Langerhans cell histiocytosis; sarcoidosis.
- **Malignant diseases**: leukemia; lymphoma; lung cancer; adenocarcinoma involving multiple organs; squamous carcinoma involving multiple organs.
- **Connective tissue diseases**: rheumatoid arthritis; Sjögren's syndrome.

Approach to Eosinophilia

Algorithm for Diagnosing Eosinophilic Disorders
Eosinophilic Lung Diseases

- Asthma
- COPD
- Eosinophilic Bronchitis
- Drug-Induced
- Fungal Airway Disease
- Eosinophilic Pneumonias
- Churg-Strauss Syndrome
- Parasitic Lung Diseases
- Diffuse Lung Diseases (e.g. Idiopathic Pulmonary Fibrosis [IPF])
- Carcinoma (e.g. Lung Cancer, Hodgkin’s Disease)
- Connective Tissue Disease (RA, Sjögren’s)
- Hypereosinophilic Syndrome (HES)
- Stem Cell or Tumor Cell Disorders

Eosinophilia Associated Lung Diseases

Conclusions

- Peripheral and/or Lung Eosinophilia is Found in a Number of Common Lung Diseases (asthma COPD) or as Incidental Findings (malignancies, CTDs)
- Initial Steps are Directed Toward R/O Extrinsic Factors (e.g. drugs, parasites)
- Key Differential Factors
  - Presence and Nature of Pulmonary Infiltrates
  - Characteristics of Onset
  - Nature of Extra-pulmonary Involvement
- Hematologic Evaluation (bone marrow) Indicated When Diagnosis Unclear
- Treatment – Corticosteroids, anti-IL-5 (biologics)

Eosinophilia Associated Lung Diseases

Questions?