THINGS THAT LOOK LIKE ASTHMA

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ASTHMA SYMPTOMS

• Wheezing
• Cough
• Dyspnea
• Nocturnal cough, dyspnea
• Increase use of rescue
THINGS THAT WALK INTO PRIVATE OUTPATIENT ALLERGY OFFICE

• Aspirin induced bronchospasm
• Churg Strauss
• Wegners
• ABPA
• Immotile cilia syndrome
ASPIRIN INDUCED BRONCHOSPASM

- A 45 year old white male with dyspnea. Shortness breath noted 1 year after viral infections. Dyspnea progressively worsened over year. Little improvement on high dose combination inhaled therapy. Improvement noted on 40-60 mg of steroid a day. Anosmia present.
- FEV1 at 70% without reversal
- Labs: peripheral eosinophilia
- PE:
  - HEENT: B/L Nasal polyps
  - Lungs: diffuse wheeze in all quarters
INTRODUCED INTO MEDICINE

- Used by Hippocrates (willow tree bark)
  - Used as antipyretic and analgesic
- 1899 Poznan, Poland, the first case of transient angioedema, urticaria after use
- 1919 reported with bronchospasm
- 1920 first death after aspirin use
- 1922 aspirin triad first reported
- 1968 triad reported by Samter and Beers
- 1970 link discovered between asthma episode and inhibition of arachidonic acid cyclooxygenase by aspirin.
AIA

- Inflammation of both upper and lower respiratory tracts
- Eosinophilic rhinosinusitis
- Nasal polyps [Anosmia]
PREVELANCE

• In general population from 0.6% to 2.5%
• In asthmatics, 4 to 11%
• In patients with asthma and nasal polyps, 30-40%
• Mostly women, 2.3 to 1
• Rare in children
• 1 to 6% have a family history of aspirin sensitivity
PATHOGENESIS

• Aspirin and NSAIDs are potent inhibitors of cyclooxygenase-1 (COX-1).
• COX-2 inhibitors tolerated by patients.
NATURAL HISTORY

• Persistent rhinosinusitis
  • Onset after flu-like infection
  • Becomes perennial
  • Becomes chronic rhinosinusitis

• Followed by nasal polyps

• Followed by aspirin hypersensitivity

• Asthma diagnosed 2-3 years later

• At about same time NSAID adverse reactions begin although tolerated before
TYPICAL REACTIONS

- Bronchospasm
- Profuse rhinorrhea
- Nasal congestion
- Sneezing
- Itching
- Ocular injection
- Tearing
- Rarely periorbital swelling
- Rash/erythema of head and neck
ASTHMA

- Protracted course despite NSAID avoidance
- Some required chronic prednisone use
EOSINOPHILS

• Significant blood and sputum eosinophils
• Bronchial biopsy shows eosinophil infiltration
• Increased IL5 positive cells
• Positive skin test to 34-64% of patients
CROSS REACTIONS WITH NSAIDS

• Sensitive to any NSAIDs that block COX1
• Ibuprofen common
• Acetaminophen at high doses may cause reversible symptoms
• COX 2 inhibitors are usable by patients but high doses may cause problems
• Adverse effects have been found with the use of hydrocortisone hemisuccinate in patients
DIAGNOSIS

• Aspirin provocation challenge
  • Oral
  • Inhalation
  • Nasal
  • intravenous
ORAL CHALLENGE

• Hospital setting
• Direct supervision
• FEV1 at least 70%
• Several asthma drugs removed
• Only oral available in US
TREATMENT

- Zileutin
- Desensitization to aspirin
A 35 year old female presents with a progressive episode of wheezing and shortness of breath. Numbness and tingling has been noted over the dorsal aspect of the left forearm. The patient required 40-60 mg of prednisone daily in order have minimal respiratory improvement.

- FEV1 = 65%
- Peripheral eosinophilia of 30%
- P-ANCA positive
- Sural nerve biopsy showed granuloma
CLINICAL CRITERIA

• Lanham's criteria (all of the following)
  • Asthma
  • Peak eosinophilia >1.5 $\times 10^9$ cells/L
  • Systemic vasculitis, two or more extrapulmonary sites

• American College of Rheumatology (4 of the following in the setting of vasculitis)
  • Asthma
  • Peak eosinophilia >10% total WBC
  • Peripheral neuropathy attributed to vasculitis
  • Transient pulmonary infiltrates
  • Paranasal sinus disease
  • Biopsy showing blood vessels with extravascular eosinophils
CLINICAL CRITERIA FOR CSS (CONTINUED)

- Chapel Hill Consensus Conference
  - Asthma
  - Peripheral Eosinophilia
  - Eosinophil-rich granulomatous inflammation involving the respiratory tract
  - Necrotizing vasculitis affecting small to medium vessels

These clinical criteria are consistent in the diagnosis of CSS. Mayo series shows 92% of subjects with CSS fulfill at least one of these classification schemes and 86% fulfill two or more (Keogh & Specks, American Journal of Medicine, 2003)
A 40 year old female presents with progressive dyspnea and wheeze that has worsened over months. Inhaled LABA/high dose-Steroids were not helpful in the control of his symptoms. Prednisone at a dose of 50mg per day where of minimal relief.

- PE: diffuse wheezing B/L
- HEENT: nasal septum perforation
- FEV1= 65%
- Peripheral eosinophilia
- C-ANCA positive
PRESENTATION

• Upper Airway (95%)
  • Persistent rhinorhea
  • Purulent/bloody nasal discharge
  • Oral and/or nasal ulcers
  • Sinus pain
  • Other: Hoarseness, stridor, earache, conductive and/or sensorineural hearing loss, otorrhea

• Lower Airway (85-90%)
  • Cough
  • Dyspnea
  • Hemoptysis
  • Pleuritic pain
  • Pulmonary consolidation and/or Pleural effusion
EPIDEMIOLOGY

- 3/100,000 patients
- Much more common in Caucasians
- M:F = 1:1
- Mean age of onset ~40 yrs
  - Occurs at any age
  - 15% at <19 yrs, but rare before adolescence
DIAGNOSIS

• Clinical Criteria:
  • Nasal or oral inflammation
  • Abnormal CXR showing nodules, fixed infiltrates, or cavities
  • Abnormal urinary sediment (microscopic hematuria +/- RBC casts)
  • Granulomatous inflammation on biopsy of an artery or perivascular area
  • 2+ yields sens. of 88%, spec. of 92%

• Laboratory Evaluation:
  • Leukocytosis
  • Thrombocytosis (>400,000/mm3)
  • Elevated ESR, CRP
  • Normochromic, normocytic anemia
• Biopsy
  • Taken from site of active disease
  • Leukocytoclastic, necrotizing vasculitis with little or no complement and IgG on immunofluorescence
  • Granulomatous inflammation differentiates from MPA
  • Kidney: segmental necrotizing GN, pauci-immune on immunofluorescence or EM

• ANCA
  • Indirect immunofluorescence assay:
    • c-ANCA or p-ANCA
    • 90-95% sensitive
  • ELISA:
    • PR3 or MPO
TREATMENT RECOMMENDATIONS

• Induction of Remission
  • Daily oral cyclophosphamide + glucocorticoids (most aggressive Rx)
  • Monthly cyclophosphamide + glucocorticoids
  • Low-dose weekly oral MTX + glucocorticoids (mild disease)
  • No role for PLEX unless DAH present

• Maintenance of Remission (12-18 mos)
  • Weekly oral MTX
  • Daily oral Azathioprine
  • Cyclophosphamide not advised 2/2 toxicity
  • Glucocorticoids should be quickly tapered off

• Treatment of Relapse - Reinduction
A 55 year old female presents with persistent cough. The cough has been episodic and treated with various courses of antibiotics and steroids. The patient has experienced dyspnea and night sweats.

PE: Diffuse wheeze in all fields.

FEV1=60%

Sputum culture grew Aspergillus.

CT showed central bronchiectasis
**ABPA** is an idiopathic inflammatory lung disease characterized by an allergic inflammatory response to the colonization of *Aspergillus fumigatus*. 
It was first described in 1952 by Hinson and coworkers and then again in 1967, when Scadding recognized an association of this disease with proximal bronchiectasis in areas previously affected by infiltrates (predominantly in the upper lobes).

The first adult case of ABPA in the United States was described in 1968.
Epidemiology

There is no gender predilection.

Majority of the cases present in the third to fifth decade of life but may also present during childhood.

The prevalence of ABPA is about 1-2% in asthma patients and 2-15% in cystic fibrosis patients.

In the past two decades, there has been an increase in the number of cases of ABPA due to the heightened physician awareness and the widespread availability of serologic assays.

In a recent meta analysis a prevalence of aspergillus hypersensitivity and ABPA in asthma of 28% and 12.9% respectively.
Pathogenesis of ABPA

Although the pathogenesis of ABPA is incompletely understood, it is believed to result from a complex immunological reaction to chronic airway colonization by aspergillus.

Inhaled spores colonize the airway, proliferate and result in chronic antigenic stimulation of the airway, tissue injury and the clinical features of ABPA.
Common signs and symptoms

• Low grade fever
• Wheezing
• Bronchial hyperactivity
• Haemoptysis
• Productive cough (often associated with brownish black mucus plugs)
**Diagnosis and Diagnostic Criteria**

Criteria Used for the Diagnosis of ABPA

*Rosenberg-Patterson criteria*

**Major criteria (mnemonic ARTEPICS)**

A = Asthma
R = Roentgenographic fleeting pulmonary opacities
T = Skin test positive for Aspergillus (type I reaction, immediate cutaneous hyperreactivity)
E = Eosinophilia
P = Precipitating antibodies (IgG) in serum
I = IgE in serum elevated (>1,000 IU/mL)
C = Central bronchiectasis
S = Serums *A fumigatus*-specific IgG and IgE (more than twice the value of pooled serum samples from patients with asthma who have Aspergillus hypersensitivity)
Minor criteria

1. Presence of Aspergillus in sputum
2. Expectoration of brownish black mucus plugs
3. Delayed skin reaction to Aspergillus antigen (type III reaction)

The presence of six of eight major criteria makes the diagnosis almost certain.
The disease is further classified as ABPA-S or ABPA-CB on the absence or presence of central bronchiectasis, respectively.
Minimal diagnostic criteria for ABPA

**Minimal ABPA-CB (Central Bronchiectasis)**
1. Asthma
2. Immediate cutaneous hyperreactivity to Aspergillus antigens
3. Central bronchiectasis
4. Elevated IgE
5. Raised *A fumigatus*-specific IgG and IgE

**Minimal ABPA-S (Serum)**
1. Asthma
2. Immediate cutaneous hyperreactivity to Aspergillus antigens
3. Transient pulmonary infiltrates on chest radiograph
4. Elevated IgE
5. Raised *A fumigatus*-specific IgG and IgE
IMMOTILE CILIA SYNDROME

• A 35 year old female presents with a persistent productive cough, bronchitis and sinusitis. She often is short of breath. She describe infections that start in the upper airways and progresses to the lower airways and at which point she develops an a pneumonia. She was infertile but able to have children by IVF.

• FEV1=70%

• PE: diffuse wheezes and ronchus noted

• Labs normal

• Nasal biopsy shows immotile cilia
1933 Dr. Kartagener

- 4 cases

- Quantified the clinical triad:
  - Bronchiectasis
  - Chronic sinusitis
  - Situs inversus

- Primary ciliary dyskinesia (PCD), formerly immotile cilia syndrome (ICS)
  - PCD patients do not have situs inversus
PCD

• The classic symptom combination associated with PCD was first described by A. K. Zivert.
PRIMARY CILIARY DYSKINESIA

- a rare, ciliopathic, autosomal recessive genetic disorder that causes a defect in the action of the cilia lining the respiratory tract (lower and upper, sinuses, Eustachian tube, middle ear) and fallopian tube, and also of the flagella of sperm in males.
SIGN AND SYMPTOMS

• The main consequence of impaired ciliary function is reduced or absent mucus clearance from the lungs, and susceptibility to chronic recurrent respiratory infections, including sinusitis, bronchitis, pneumonia, and otitis media.

• Progressive damage to the respiratory system is common, including progressive bronchiectasis beginning in early childhood, and sinus disease (sometimes becoming severe in adults).

• In males, immotility of sperm can lead to infertility, although conception remains possible through the use of in vitro fertilization and, as well as this, there have been reported cases where sperm were able to move.

• Trials have also shown that there is a marked reduction in fertility in female sufferers of Kartagener's Syndrome due to dysfunction of the oviductal cilia.
GENETICS

- PCD is a genetically heterogeneous disorder affecting motile cilia which are made up of approximately 250 proteins.
- Around 90% of individuals with PCD have ultrastructural defects affecting protein(s) in the outer and/or inner dynein arms which give cilia their motility, with roughly 38% of these defects caused by mutations on two genes, DNAI1 and DNAH5, both of which code for proteins found in the ciliary outer dynein arm.
WHAT’S THE PROBLEM?

• Dynein arms do not function
  • Immotile cilia/flagella

• Consequences
  • 50% result in situs inversus
  • Symptoms similar to cystic fibrosis
  • Constant infection in lungs and sinuses

• Dysfunctional cilia!!
DYNEIN ARM DEFECTS

- 18 ultrastructural defects identified
- Most common
  - Outer dynein arm
  - Inner dynein arm
  - Radial spokes
  - Absence of nexin links

Geremek et al. 2004
TREATMENT

• Sputum culture to determine type of infection
  • Prescribe effective antibiotics
  • Chest Vest
  • Inhaler
  • Nebulizer
TAKE HOME POINTS

• If it looks like asthma:
• But does not respond to traditional therapy:
• Think!