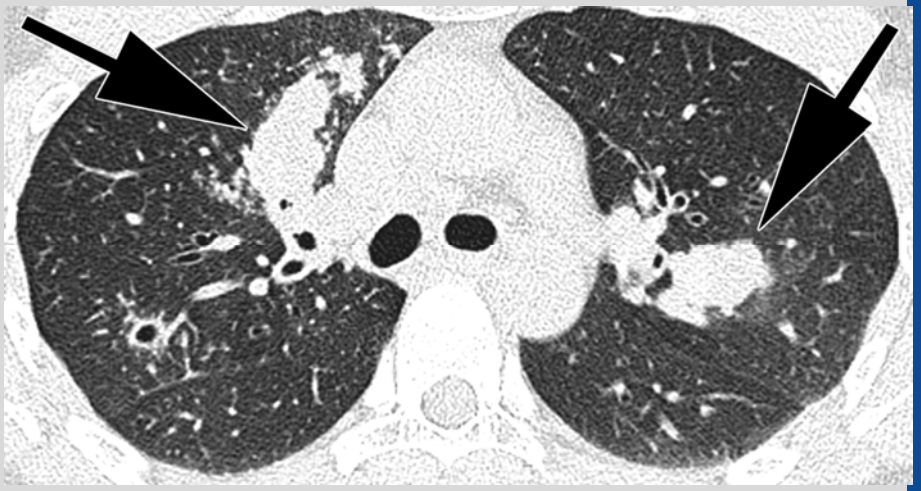

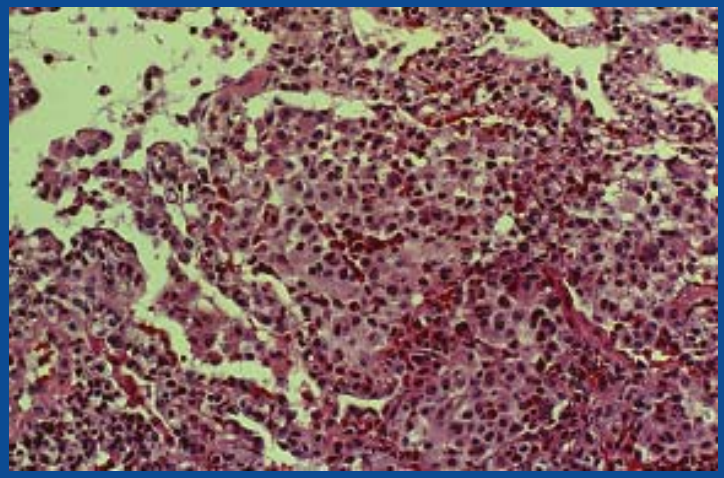

Allergic Bronchopulmonary Aspergillosis and Eosinophilic Lung Disease

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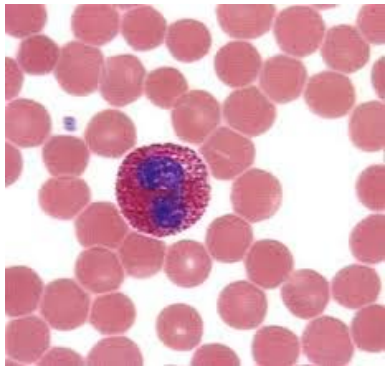
DISCOVERY | INNOVATION | CURE

HARVARD MEDICAL SCHOOL

Eosinophils



- Bone marrow-derived granulocytes
- Arise from myeloid progenitor shared with basophils
- Major distribution in tissues (gut, not respiratory)
- Production in marrow increases selectively in helminth infections, allergic disease, certain tumors
- Involved in elimination/containment of certain helminths
- Signature of allergic inflammation; frequently found in fibrotic/remodeling tissues, tumors

Eosinophil effector systems and functions

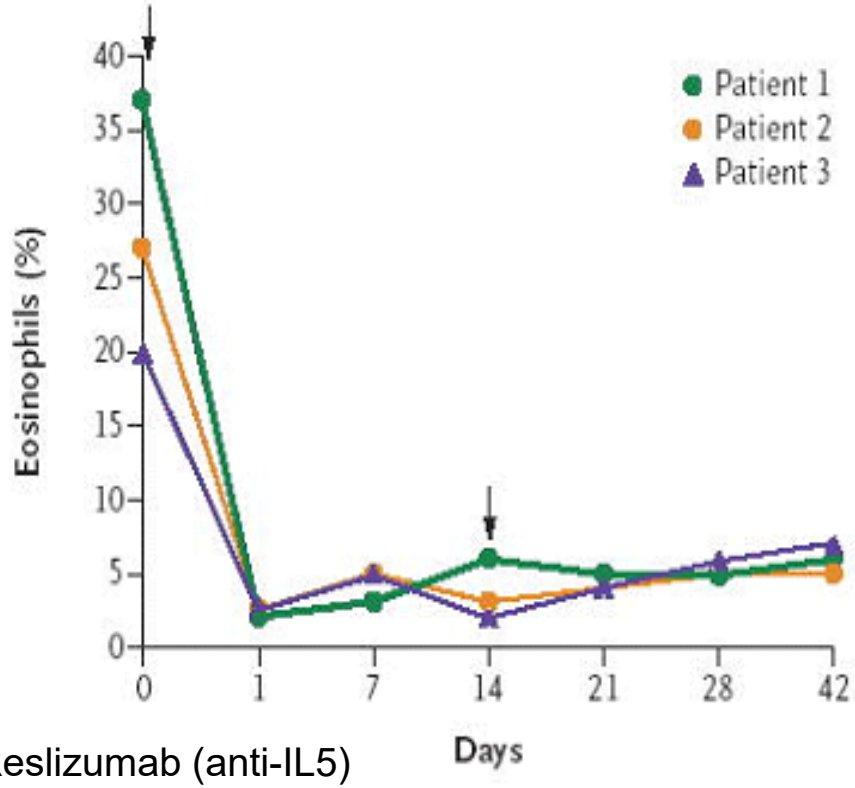
- Cationic granule proteins (MBP, ECP, EDN, EPO, CLC)- neurotoxic, epithelial damage, helminthicidal
- Cytokines (too many to mention-TGFβ is prominent)- proinflammatory, pro-fibrotic
- Lipid mediators; 5-LO (leukotrienes), 15-LO (15-HETE and products), COX (PGD_2)- bronchoconstriction, vascular leak, effector cell recruitment

Eosinophil development

- Regulated by eosinophilopoietic cytokines (IL-3, GM-CSF, IL-5*); produced mainly by T cells
- Overlapping functions, but different cellular targets (IL-3, GM-CSF act on multiple lineages; only IL-5 is selective for eosinophils)
- Receptors composed of ligand-specific α subunits and a shared β subunit
- All three sustain survival, augment effector functions, and reduce centrifugation density (“hypodense” eosinophils)
- IL-5 is an eosinophil-selective terminal differentiation factor and a mobilization factor from marrow
- Eosinophil migration to tissues requires cooperation between IL-5 plus CCR3-binding chemokines (eotaxins 1, 2, and 3; MCP3, RANTES)

*Clutterbunk et al., Blood 1989

Sustained reduction in blood eosinophil counts in patients with hypereosinophilic syndrome (HES) in response to anti-IL-5 (mepolizumab)



Mepolizumab, Reslizumab (anti-IL5)
Benrilizumab (anti-IL-5Rα)

Plotz SG, NEJM 2003

Eosinophil-associated disease processes

- Helminth infection
- Hypersensitivity reactions (e.g., DRESS)
- Tumors (lymphomas)
- Organ-specific diseases (eosinophilic lung disease, GI disease, fasciitis, myositis, cellulitis)
- Systemic mastocytosis (15% have eosinophilia)
- HES

Eosinophilic lung diseases

Asthma-associated

- Allergic bronchopulmonary aspergillosis (ABPA)
- Chronic eosinophilic pneumonia (CEP)
- Eosinophilic granulomatosis and polyangiitis (EGPA, formerly Churg-Strauss syndrome)

Non-asthma-associated

- Acute eosinophilic pneumonia (AEP)
- Simple pulmonary eosinophilia (Loeffler's)
- Tropical eosinophilia (filariasis)

*Note: pulmonary eosinophilia may occur as a secondary finding in numerous systemic autoimmune, infectious and malignant diseases

Illustrative case 1

17-year-old male with type 1 diabetes, nut allergy and longstanding mild asthma (albuterol only) presents for evaluation of worsening asthma control

- 6 month history of worsening symptoms; wheeze, dyspnea, productive cough (brown sputum, occasional blood tinge)
- Prompt improvement with oral steroids but rapid recrudescence with cessation
- Denies travel, fevers, night sweats, weight loss
- Meds: Insulin, albuterol PRN (use of 1 cannister/month)

Illustrative case 1

Exam:

- Alert, oriented, NAD
- Vital signs unremarkable, Sa02 96%
- Boggy, edematous turbinates, no polyps

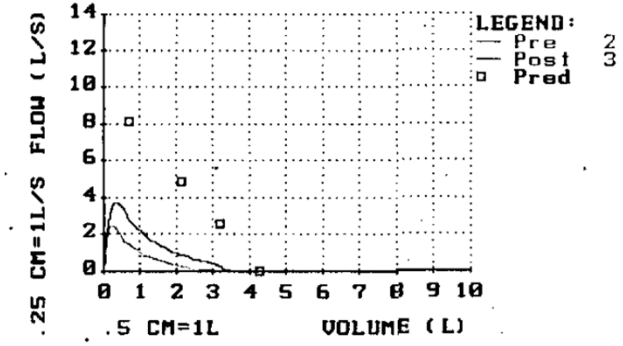
- Diffuse wheezing, fair air entry

- No clubbing

Illustrative case 1

Labs:

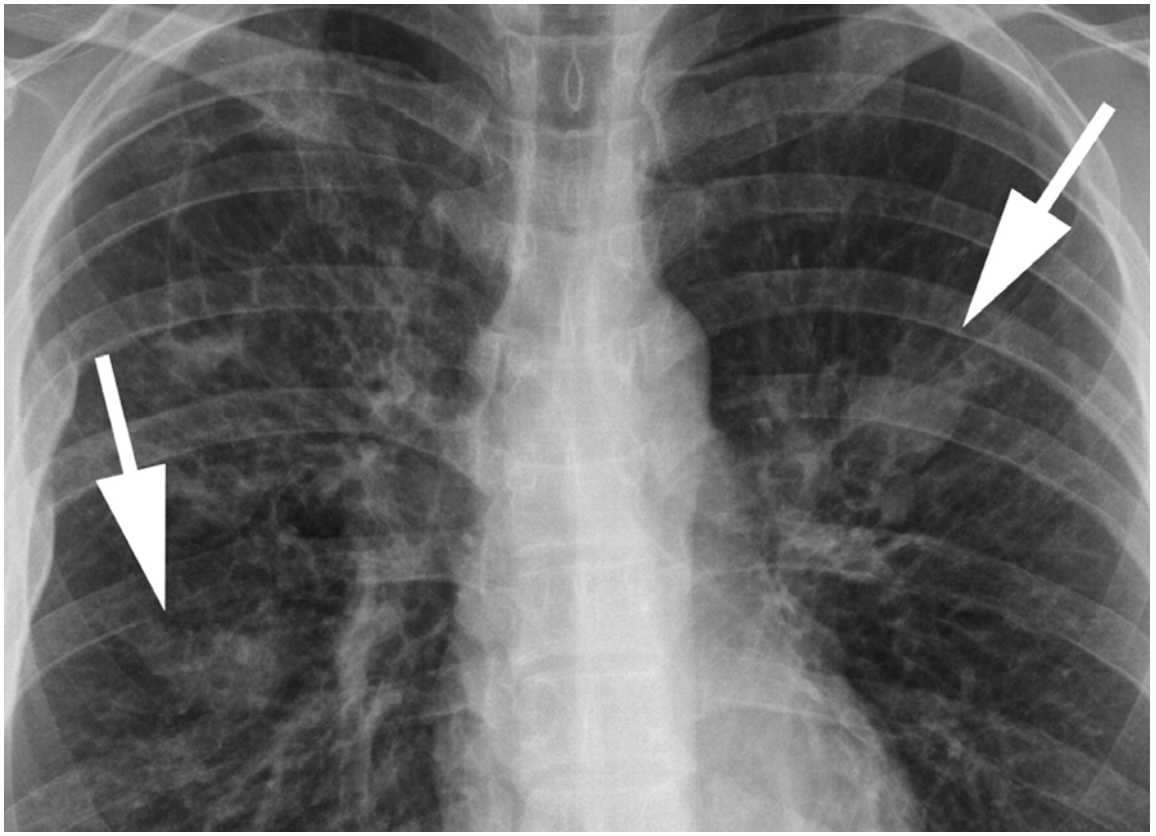
- CBC: Hct 45.7, WBC 6,270 (15% eos, TEC 940)
- IgE: 36,700
- Aspergillus SPT; 22 mm wheal, 45 mm flare
- A. fumigatus precipitins; positive
- *CFTR* mutations; none



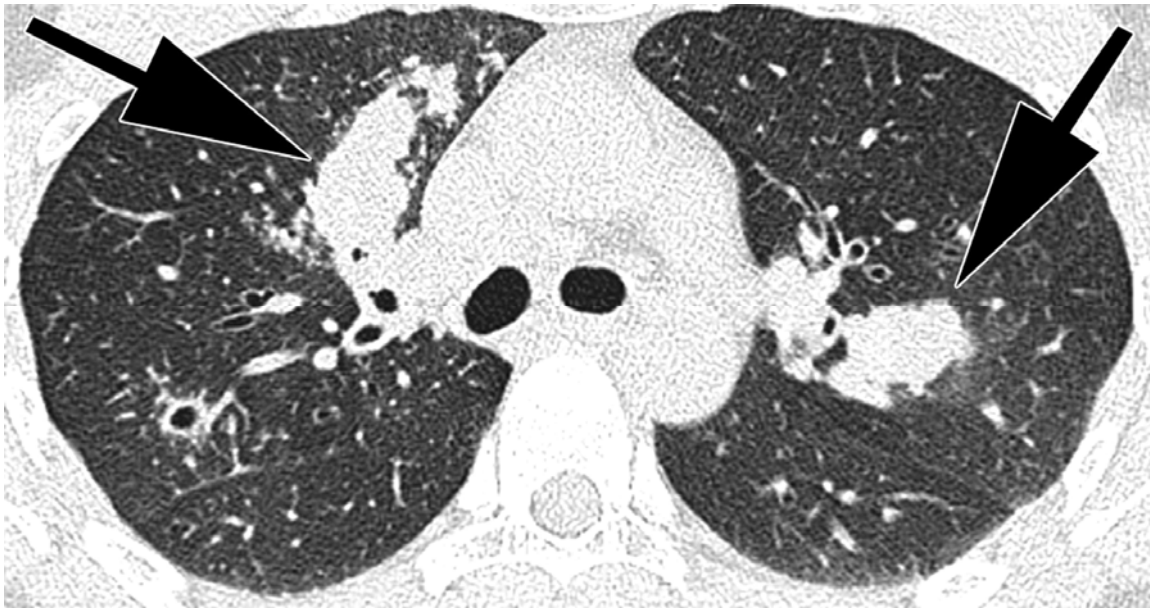
FVC = 3.22 L (74% of pred)
FEV1 = 1.36 L (33% of pred)

Increases of 9 and 46% after albuterol

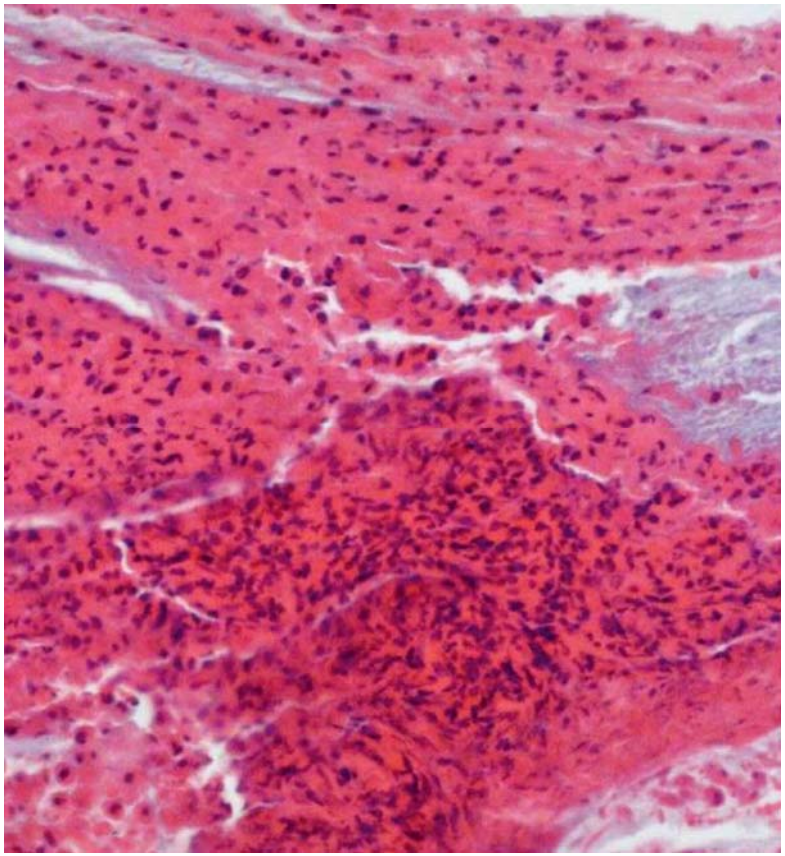
CXR-Case 1



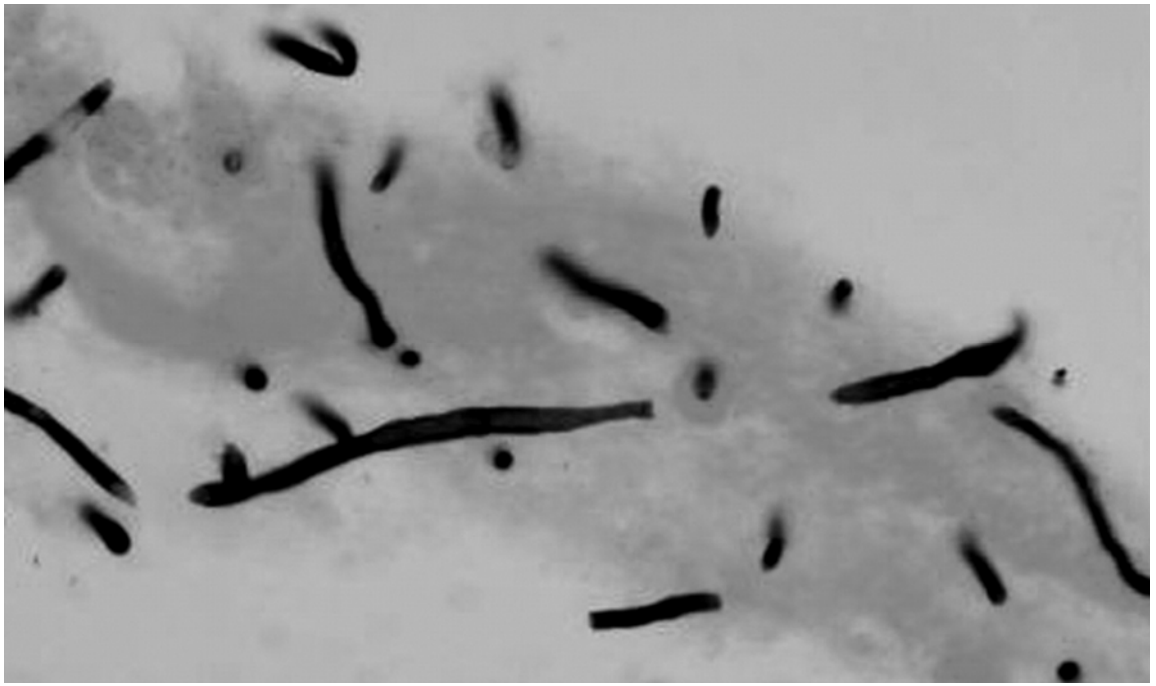
CT-Case 1



Bronchial cast- ABPA



Silver stain, bronchial cast



ABPA

(International Society for Human and Animal Mycology (ISHAM) working group)

Obligatory

- Asthma (or CF)
- Immediate cutaneous hypersensitivity to *Aspergillus fumigatus*
- Total serum IgE >1000 ng/ml

PLUS

At least two of the following:

- Precipitating IgG (positive precipitins) to *Aspergillus*
- Fleeting pulmonary infiltrates
- Total eosinophil count in excess of 500 (may be historical)

New proposed criteria (Asano, et al. JACI 2020)

1. Current or previous history of asthma or asthmatic symptoms
2. Peripheral blood eosinophilia (>_500 cells/mm3)
3. Elevated total serum IgE levels (>_417 IU/mL)
4. Immediate cutaneous hypersensitivity or specific IgE for filamentous fungi
5. Presence of precipitins or specific IgG for filamentous fungi
6. Filamentous fungal growth in sputum cultures or bronchial lavage fluid
7. Presence of fungal hyphae in bronchial mucus plugs
8. Central bronchiectasis on CT
9. Presence of mucus plugs in central bronchi, based on CT/bronchoscopy or mucus plug expectoration history
10. High attenuation mucus in the bronchi on CT

(Patients that meet 6 or more of these criteria are diagnosed with ABPM)

ABPA

Predisposing factors:

- Asthma, CF
- Heterozygous CFTR mutants maty be at increased risk
- HLA-DR2 (DRB1*1503) increases risk; HLA-DQ2 protects
- *SPA-2* variants correlate with severity
- *IL10* and *IL4RA* variants correlate with incidence

ABPA

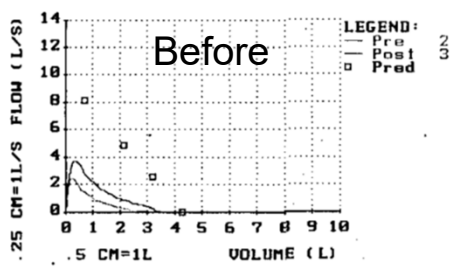
Treatment:

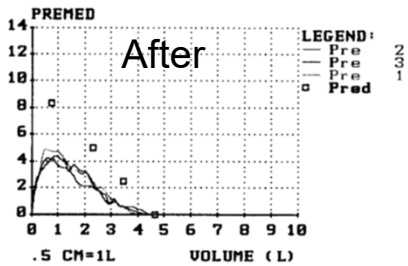
- Systemic glucocorticoids
- Itraconazole
- Omalizumab (several case reports; no RCT)
- Single case report of apparent efficacy of mepolizumab (Respir Med Case Rep. 2019; 26: 59–62.)
- RCTs ongoing for dupilumab, benrilizimab, antifungals

Illustrative case 1

Follow-up:

- Clinically improved after prolonged course (6 weeks) of oral steroids but glycemic control problematic
- Nasal polyp developed once off prednisone
- IgE fell to 16,300 from 36,700
- Eosinophilia remains <100 on 7.5mg daily prednisone, Symbicort, montelukast
- Lost to follow up after 2 years





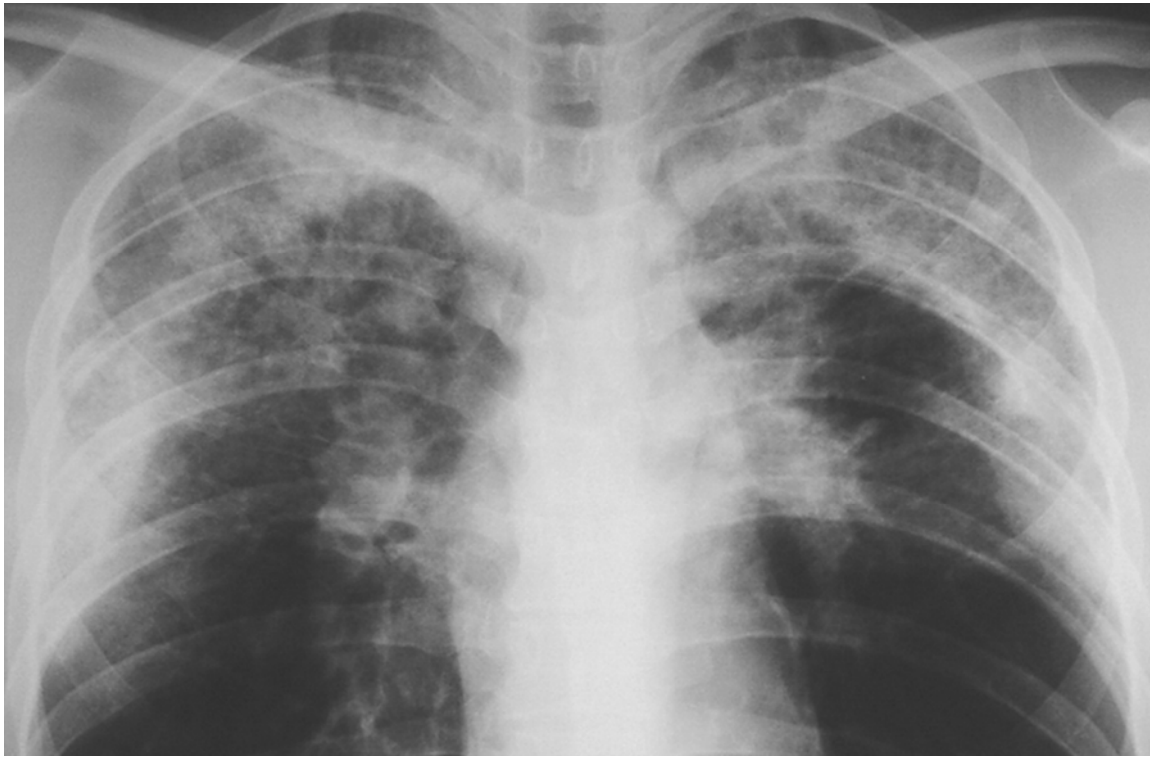
FVC = 4.59 L (98% of pred)
FEV1 = 2.78 L (69% of pred)

Illustrative case 2

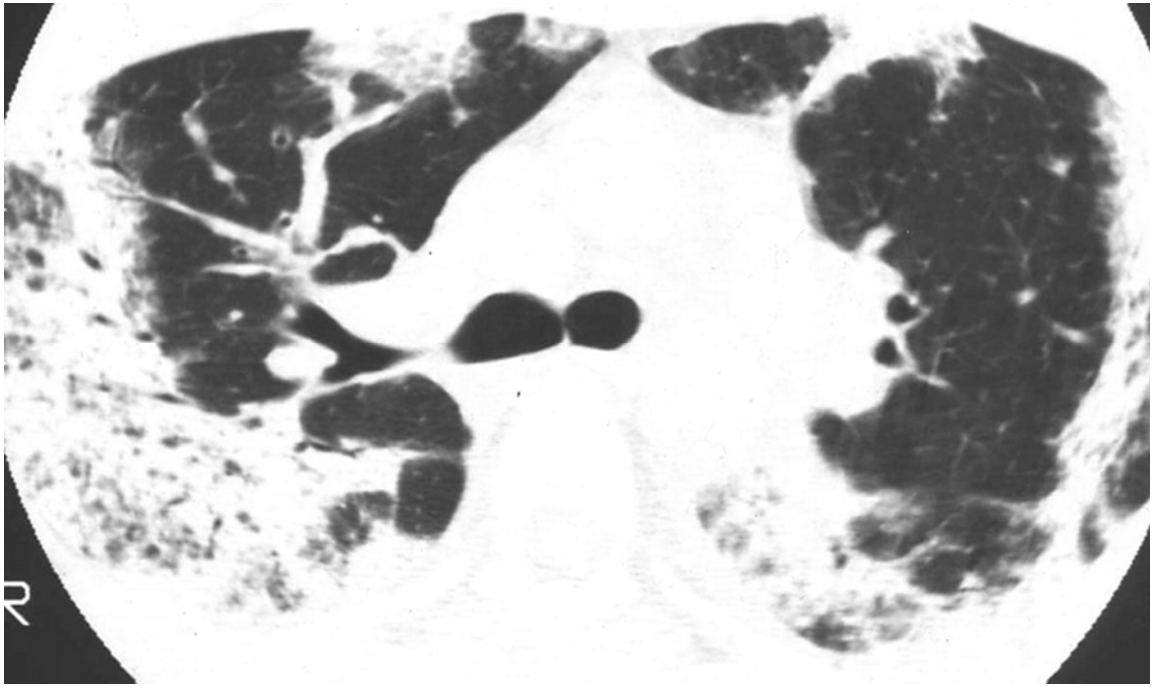
29-year-old male with longstanding asthma

- 3-month history of productive cough, wheeze, dyspnea- no improvement with antibiotics
- Recent 10-pound weight loss, night sweats
- Labs: significant eosinophilia (WBC 6,700, 27.5% eosinophils); Total IgE 127, skin testing positive for *Aspergillus* but precipitins negative

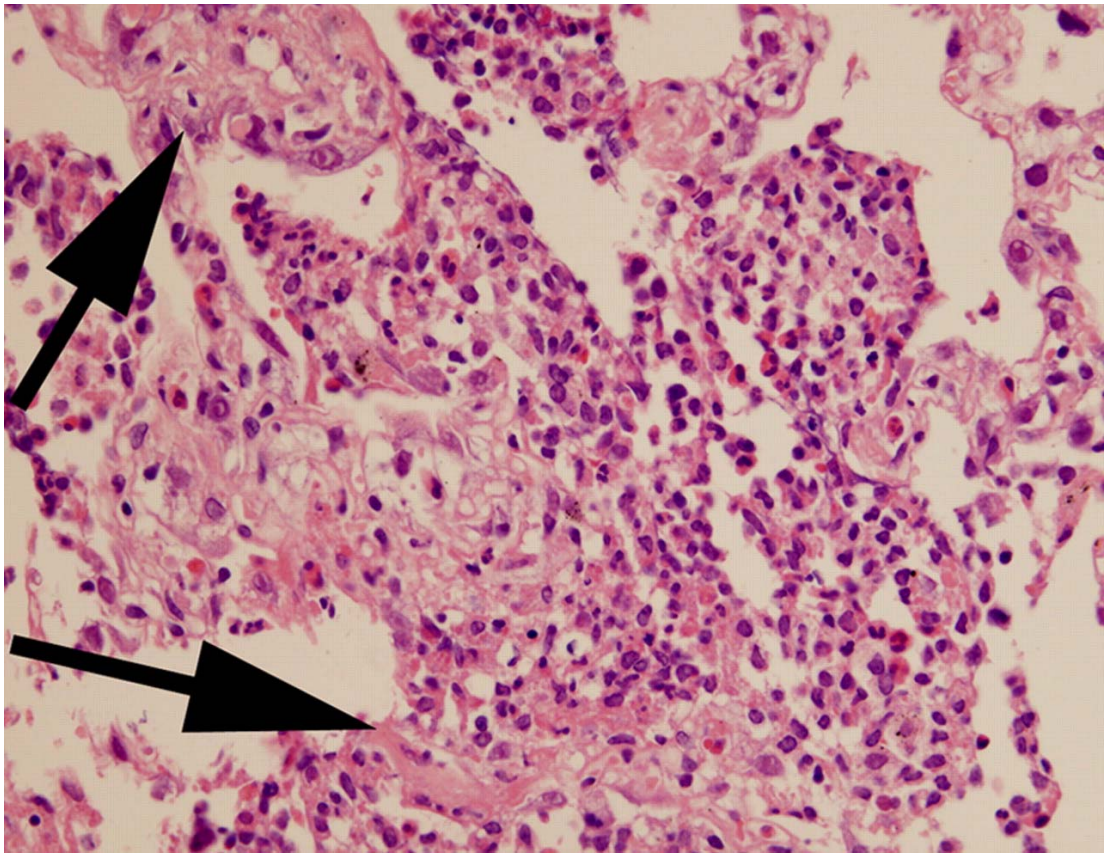
CXR-Case 2



CT-Case 2



Lung biopsy-Case 2



Chronic Eosinophilic Pneumonia (CEP)

- First reported in 1968 (Carrington, NEJM)
- Usually middle aged asthmatics
- Indolent, slowly progressive
- Blood eosinophilia common but not uniform
- BAL fluid eosinophilia
- Alveolar filling with eosinophils, macrophages
- Fibrosis with longstanding disease
- Steroid-responsive, high rate of recurrence
- Isolated case reports of treatment with mepolizumab (no RCT)

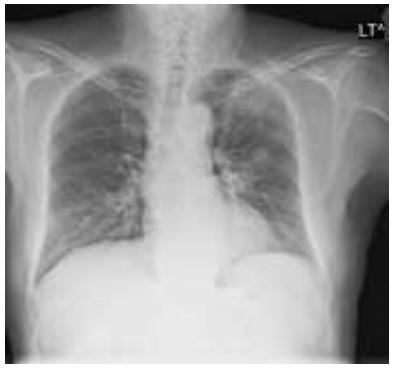
Illustrative Case 3

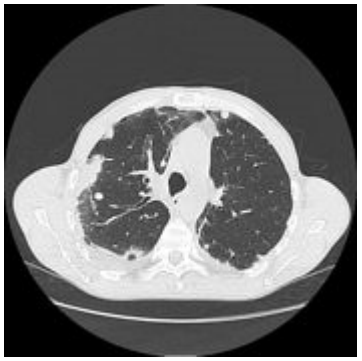
34-year-old male with longstanding history of asthma and allergic rhinitis presents with worsening dyspnea, cough, one episode of mild hemoptysis

- Worsening sinus congestion, epistaxis
- Recent nocturnal fevers, numbness of left hand
- Abdominal pain and rash (nodules)
- Exam: palpable nodules on lower extremities, diffuse wheezing, nasal polyps
- CBC: HCT 29, WBC 8600, 15% eos (AEC 1290), IgE 675, ANCA negative, CRP 36

Illustrative Case 3

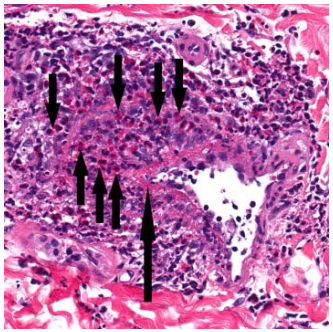
No “classical” radiographic features (nodules, infiltrates, sometimes peripheral)





Skin biopsy:

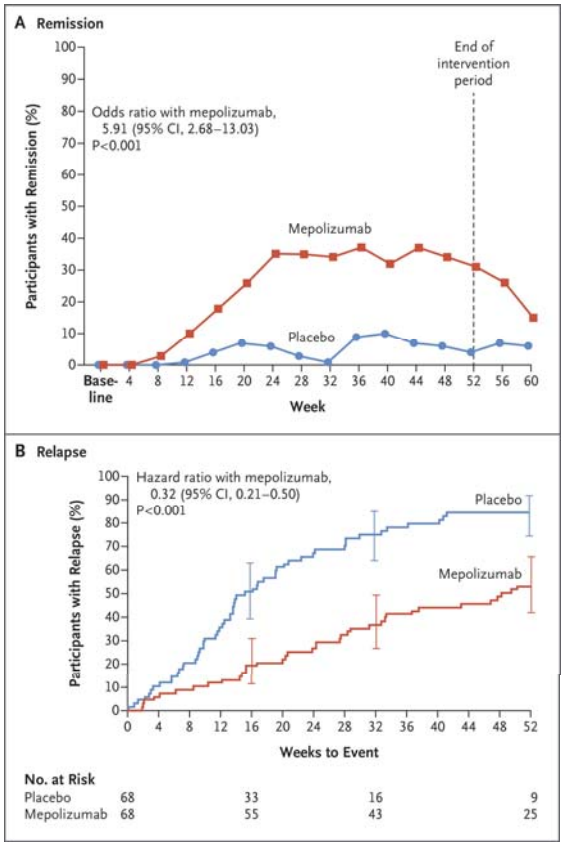
Necrotizing small vessel vasculitis with extravasated eosinophils

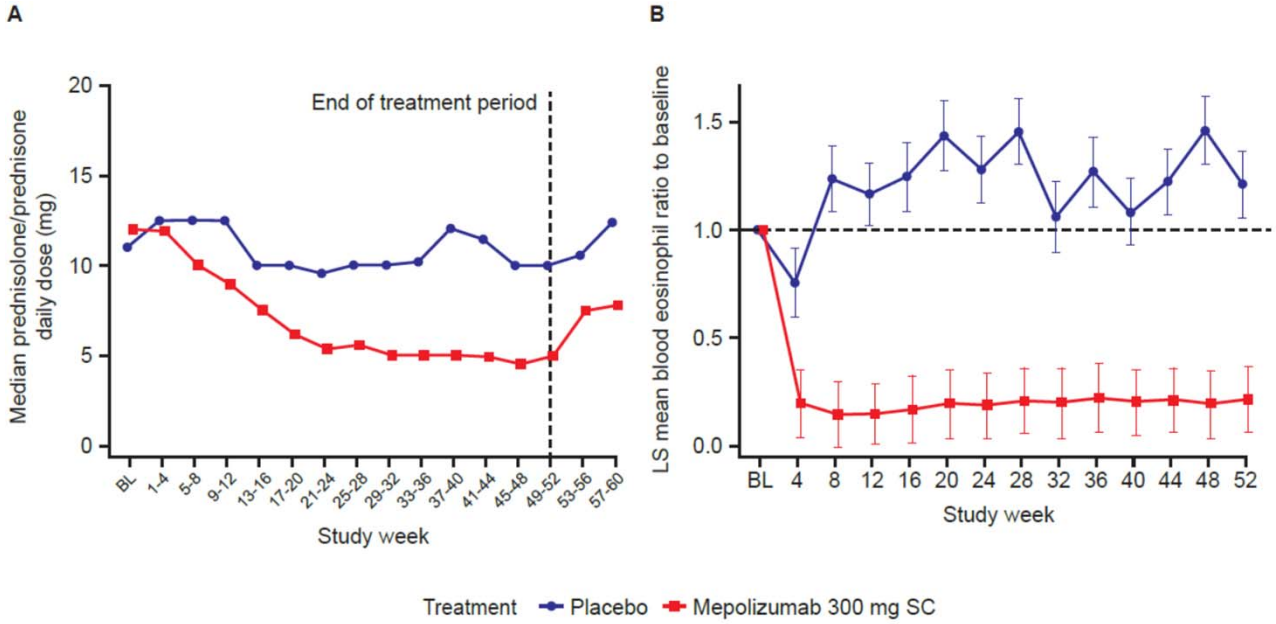


EGPA diagnostic criteria

American College of Rheumatology classification criteria (1990) ‡
Asthma
Eosinophilia >10% of total WBC
Neuropathy
Pulmonary infiltrates nonfixed
Paranasal sinus abnormalities
Extravascular eosinophils
Revised Chapel Hill Consensus Conference Nomenclature of Vasculitides (2012)
Eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract, and necrotizing vasculitis predominantly affecting small-to-medium vessels, and associated with asthma and eosinophils. ANCA is more frequent when glomerulonephritis is present.

Mepolizumab for EGPA (FDA approved in 2019)





Weschler, M. et al, NEJM 2019

CONCLUSIONS

Eosinophilic lung disorders

- Asthma-associated; ABPA, CEP, EGPA
- Not asthma-associated; AEP, Loeffler's, tropical eosinophilia
- Suspect diagnoses in patients with loss of asthma control, eosinophilia, or (in the case of EGPA) prominent extrapulmonary symptoms
- Eosinophilia is the common thread; associated lab, radiographic, and clinical features help distinguish
- Anti-IL-5 efficacious for EGPA; await studies in other disorders