PULMONARY INFILTRATES WITH EOSINOPHILIA

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15/10/10
Eosinophil cationic protein
Eosinophil peroxidase
Eosinophil-derived neurotoxin
  Cytotoxic effects
  Cell activation

Lipid mediators
  Platelet-activating factor
  Leukotriene C₄

Major basic protein

Chemokine receptor
  Chemoattraction
  Cell activation

Cytokines
  Hematopoiesis
  Chemoattraction
  Proinflammatory effects
  Tissue remodeling
<table>
<thead>
<tr>
<th>Eosinophil-associated esophagitis</th>
<th>Intrinsic disorders</th>
<th>Extrinsic disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary EE (≥15 eosinophils per high-power field without GERD)</td>
<td>Mutations of hematopoietic stem cells</td>
<td>Cytokines released by T cells</td>
</tr>
<tr>
<td>Atopic</td>
<td>Chronic eosinophilic leukemia</td>
<td>Allergic diseases</td>
</tr>
<tr>
<td>Nonatopic</td>
<td>Acute myeloid leukemia</td>
<td>AD</td>
</tr>
<tr>
<td>Familial</td>
<td>Chronic myeloid leukemia</td>
<td>Urticaria</td>
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<tr>
<td>Secondary</td>
<td>Myelodysplastic syndromes</td>
<td>Drug reactions</td>
</tr>
<tr>
<td>Eosinophilic disorders</td>
<td>Idiopathic HES</td>
<td>Autoimmune diseases</td>
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<tr>
<td>Eosinophilic gastroenteritis</td>
<td></td>
<td>BP</td>
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<tr>
<td>HES</td>
<td></td>
<td>Dermatitis herpetiformis</td>
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<tr>
<td>Noneosinophilic disorders</td>
<td>Infectious diseases</td>
<td></td>
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<tr>
<td>Iatrogenic</td>
<td></td>
<td>HIV</td>
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<tr>
<td>Infection (typically helminthic)</td>
<td></td>
<td>Ectoparasitosis</td>
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<td>GERD</td>
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<td>Insect bites</td>
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<tr>
<td>Esophageal leiomyomatosis</td>
<td></td>
<td>Erythema chronicum migrans</td>
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<tr>
<td>Connective tissue disease (scleroderma)</td>
<td></td>
<td>Erythema toxicum neonatorum</td>
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<tr>
<td>Eosinophil-associated gastroenteritis</td>
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<td>Hyper-IgE syndrome (Job syndrome)</td>
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<td>Primary (mucosal, muscularis, and serosal forms)</td>
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<td>EPF</td>
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<tr>
<td>Atopic</td>
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<td>Granuloma annulare</td>
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<tr>
<td>Nonatopic</td>
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<td>Angiolymphoid hyperplasia with eosinophilia</td>
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<tr>
<td>Familial</td>
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<td>Eosinophilic fasciitis</td>
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<tr>
<td>Secondary</td>
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<td>Eosinophilic cellulitis (Wells syndrome)</td>
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<tr>
<td>Eosinophilic disorders</td>
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<td>HES</td>
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<tr>
<td>HES</td>
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<td>Inflammatory clonal T-cell disease</td>
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<tr>
<td>Noneosinophilic disorders</td>
<td></td>
<td>Cutaneous T-cell lymphoma</td>
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<tr>
<td>Celiac disease (typically not responsive to gluten avoidance alone)</td>
<td></td>
<td>Langerhans cell histiocytosis</td>
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<tr>
<td>Connective tissue disease (scleroderma)</td>
<td></td>
<td>B-cell lymphomas</td>
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<tr>
<td>Iatrogenic</td>
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<td>Hodgkin lymphomas</td>
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<tr>
<td>Infection</td>
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<td>Acute T-cell leukemia/lymphoma</td>
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<tr>
<td>Inflammatory bowel disease</td>
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<td>Vasculitis (CSS)</td>
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*J Allergy Clin Immunol*  July 2010
• PIE $\rightarrow$ > 1000/mm$^3$ + Suggestive radiology

**BAL**
• N < 1% eosinophil

• ICEP > 40% , IAEP > 25%

• 3-40% $\rightarrow$ IPF, CTD-ILD, HP, sarcoidosis, BA, pneumoconiosis, infection

• Eosinophilic pneumonia $\rightarrow$ predominant cell eosinophil & > 25% ( >40% ) of DLC
Gold standard - Seldom necessary

Eosinophils

Macrophages

Eosinophilic granules

Charcot leydon crystals

Eosinophilic microabscess

Global architecture of lung remains normal

Vasculitis (usually non necrotising)

DAD, fibrinous exudates
Churg- Strauss syndrome (CSS)

- Eosinophil-rich and granulomatous inflammation.
- Necrotizing vasculitis affecting small to medium-sized vessels.
- Associated with asthma and eosinophilia.
- Possible defects in regulatory CD4+ CD25+ or CD4+ CD25- T-cell lymphocytes (producing IL-10 and IL-2) in CSS.
- ANCA + in 40 %
LTR, Omalizumab

Vasculitis
38-49 yr

Tissue eosinophilia

Asthma & rhinitis
35 yr
Pulmonary manifestations

• Prodromic & eosinophilic phase
• Long standing asthma
• Loeffler’s like syndrome in 40% of pt
• Migratory, nonlobar, peripheral pulmonary infiltrates
• Nodular lesions (noncavitating)
• B/L pleural effusion
• Asthenia, weight loss, fever, arthralgias, and myalgias → often herald the development of the extrapulmonary manifestations of vasculitis.

• CCF – eosinophilic myocarditis/coronary arteritis/DCM

• Eosinophilic vasculitis in transplanted heart.

• Pericardial effusion/VTE

• Endomyocardial rare.
• Rhinitis/sinusitis (75%)
• PNS/CNS
• GIT
• Renal (26%)
• Dermatological (50%)
• Rheumatological
American College of Rheumatology criteria

Sensitivity 85% Specificity 99.7%

If 4/6 present in a patient with proven systemic vasculitis.

- Asthma.
- Eosinophilia >10% DLC.
- Mononeuritis (including multiplex) or polyneuropathy.
- Fluctuating opacities on chest x-ray.
- Bilateral maxillary sinusal abnormalities.
- Presence of extravascular eosinophils on a biopsy including a vessel.
ANCA +ve vasculitic phenotype

- 38%
- Renal
- DAH
- Purpura
- PNS
- Vasculitic phenotype

ANCA –ve tissue disease phenotype

- 62%
- Cardiac
- Lung (except DAH)
- Eosinophilic lesion/organ fibrosis

FFS

- Proteinuria greater than 1 g/day.
- Renal insufficiency, serum creat> 1.58 mg/Dl.
- Gastrointestinal tract involvement
- Cardiomyopathy
- Central nervous system

• FFS = 0 → Steroids ± MTX

• FFS >0 → Pulse methypred+ 12 cycles of CYC

Taper/stop steroids ± Azathioprine/MTX

18-24 months

Rituximab → role in ANCA +; bronchospasm in ANCA –ve


• Imatinib

• Anti IL-5/Mepolizumab


• Infliximab/Etarnecept
ICEP (Idiopathic chronic eosinophilic pneumonia)

- Female: male - 2:1
- 45 yrs
- ?Smoking protective
- H/O atopy in half
- Asthma 2/3 of pt
Clinical features

- SOB X mths
- Chest pain
- Dry cough → min mucoid sputum
- Hemoptysis (10%)
- Wt loss = 10 kg (10%)
- URT (rhinitis/sinusitis)
- Wheeze 1/3 rd
Peripheral consolidation with eosinophilia

- CEP
- SPE
- CSS
- Drug induced
- Sarcoidosis
- DIP
• ↑ESR, ↑ IgE

• ↑ ↑ urinary EDN (eosinophil degranulation)

• PFT → obstructive/restrictive

• T/t → steroids ; dramatic response

  >6 mth / relapses
IAEP

- 1. Acute onset of febrile respiratory manifestations (<1 mth)
- 2. Bilateral diffuse opacities on chest radiography
- 3. Hypoxemia, with PaO2 on room air < 60 mm Hg, and/or PaO2/FiO2 <300 mm Hg, and/or sPO2 on room air < 90%
- 4. Lung eosinophilia, with >25% eosinophils on BAL DLC (or eosinophilic pneumonia at lung biopsy)
- 5. Absence of infection, or of other known causes of eosinophilic lung disease (especially drug induced)

• Average age -30 yr but can be <20/>40
• Male
• <7 to <30 days
• Asthma-/atopy ±
• Recent alterations in smoking habits seem to play a major role in the onset of “idiopathic” AEP.
• Outdoor activities??

  Chest 2008; 133:1174-1180.

• Increased levels of (1 3)-beta-D-glucan (a major component of the cell wall of most fungi and also one of the components of cigarette smoke) have been reported in BAL fluid

  Chest 2007; 131:1234-1237.
• Peripheral AEC- <300; may↑↑ during course
• BAL eosinophil 37-54%
• PFT - restrictive
• MV/NIV is necessary in a majority of patients for ALI or ARDS.
• shock is exceptional; extrapulmonary organ failure does not occur.
• T/t → methylprednisolone; spontaneous
• Prognosis better than ALI/ARDS
Hypereosinophilic syndrome

<table>
<thead>
<tr>
<th>Old definition: idiopathic hypereosinophilic syndrome</th>
<th>Proposed new definition: HESs</th>
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</thead>
<tbody>
<tr>
<td>1. Blood eosinophilia of greater than 1500/mm³ for at least 6 mo</td>
<td>1. Blood eosinophilia of greater than 1500/mm³ on at least 2 occasions or evidence of prominent tissue eosinophilia associated with symptoms and marked blood eosinophilia</td>
</tr>
<tr>
<td>2. Unknown trigger of eosinophilia</td>
<td>2. Exclusion of secondary causes of eosinophilia, such as parasitic or viral infections, allergic diseases, drug-induced or chemical-induced eosinophilia, hypoadrenalism, and neoplasms</td>
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<tr>
<td>3. Signs and symptoms of organ involvement</td>
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Available in most hospital settings
- Complete blood count with leukocyte differential
- Microscopic examination of peripheral blood smear
- Serum IgE
- Serum IgG, IgA, IgM
- Serum Vitamin B12
- Leukocyte alkaline phosphatase score
- Bone marrow smear and biopsy (with staining for tryptase and reticulin)
- Lymphocyte phenotyping
- TCR gene rearrangement analysis (Southern blot and polymerase chain reaction)
- Conventional cytogenetic analysis on peripheral blood and bone marrow
- Abdominal ultrasound (measurement of liver and spleen)
- Echocardiogram and cardiac magnetic resonance imaging when possible

Investigations referred to qualified laboratories
- Serum tryptase
- Serum TARC (thymus and activation-regulated chemokine)
- FIP1L1-PDGFRα fusion
- RT-PCR, FISH
- Lymphocyte phenotyping*
  including CD2, CD3, CD4, CD5, CD6, CD7, CD8, CD25, CD27, CD45RO, TCRα/β, TCRγδ, HLA-DR, CD95
- TCR gene rearrangement analysis*
  eventually on a FACS-sorted phenotypically aberrant population
- Conventional cytogenetic analysis*
  in presence of rIL-2 in addition to usual mitogens
- Cytokine profile of T-cell populations
  IL-4, IL-5, IL-13, IL-3, GM-CSF
  intracellular cytokines at the single cell level by flow cytometry
cytokines in PBMC culture supernatants
Treatment

• m-HES $\rightarrow$ imatinib mesylate 100-400 mg/d
  side effects- nausea, vomiting, fluid overload
  cardiotoxic

• L-HES $\rightarrow$ corticosteroids

• Prognosis

  survival 12% at 3 yrs $\rightarrow$ 70% at 10 yrs
Novel Therapies

- Nilotinib
- dasatinib
- Sorafenib
- PKC412

- Anti-IL5 therapies:
  - mepolizumab
  - reslizumab

- Alemtuzumab: anti-CD52 Mab

The Norwegian journal of medicine 2010;68:7/8
Loeffler syndrome (SPE)

- a/k/a Simple pulmonary eosinophilia
- Any age
- Self limiting resp symptoms
- Mod- marked eosinophilia
- ?hypersensitivity to ascaris lumbricoides
• PFT – restrictive; dec DLco
• Stool R/E- WNL until 8 weeks of onset of respiratory syndrome → so F/U over 3 mth period
• Search for other etiology
• T/t → bronchodilators ± steroids ± mebendazole
• Eosinophilic pneumonia due to parasites almost always occurs during larval migration to the lungs.
• Initially (in the pulmonary infiltrate phase) parasitological stool examination results are negative, because the worms are still in the larval phase and therefore do not produce eggs.
• Stool examination results remain negative for up to 8 weeks after the onset of pulmonary symptoms.
Tropical pulmonary eosinophilia

- 2nd-3rd decade
- Males
- C/F- immune response of the host to the parasites.
- Nocturnal cough ± SOB/wheeze
- LOA/fever
• do not usually have clinical features of lymphatic filariasis.

• Microfilariae are usually not found in the blood or the lung. The circulating microfilariae are trapped in the lung vasculature where they release their antigenic contents, further triggering the inflammatory pulmonary reaction.
• BAL(54%) & blood(2000) eosinophilia
• IgE levels >10,000 ng/mL
• ↑↑ antifilarial IgG.
• Persisting irregular basilar opacities in 2/3 of patients after 1 year.
• “reticulonodular pattern” in majority of patients ±bronchiectasis/air trapping/mediastinal lymphadenopathy
• T/t → DEC 2mg/kg tds X 2-3 weeks ± steroids
Diagnostic criteria

- cough worse at night
- residence in a filarial endemic area
- eosinophil count > 3300 cells/mm³
- clinical and hematologic response to DEC

Strongyloidosis

• Loeffler’s like symptoms following transcutaneous infection
• Chronic → by autoinfection → recurrent asthma like symptoms which worsen with steroid
• Hyperinfection syndrome in defective CMI/GI disorder → prolong therapy
• Ivermectin/thiabendazole/albendazole
• Ankylostomiasis → creeping eruption
  self limiting (no specific T/t)

• Toxocara canis → visceral larva migrans
  ↑ TLC, IgG & E, hepatomegaly
  self limiting
  albendazole/steroids hasten recovery
<table>
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<tr>
<th>Drugs with Typical Pulmonary Eosinophilia</th>
<th>Drugs with Occasional Pulmonary Eosinophilia</th>
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<tbody>
<tr>
<td>Acetylsalicylic acid</td>
<td>Bleomycin</td>
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<td>Captopril</td>
<td>Carbamazepine</td>
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<tr>
<td>Diclofenac</td>
<td>Chlorpromazine</td>
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<tr>
<td>Ethambutol</td>
<td>Cocaine</td>
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<tr>
<td>Fenbufen</td>
<td>Desipramine</td>
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<tr>
<td>Granulocyte-macrophage colony-stimulating factor</td>
<td>Dapsone</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Febarbamate</td>
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<tr>
<td>Minocycline</td>
<td>Gold salts</td>
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<tr>
<td>Naproxen</td>
<td>Heroin</td>
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<tr>
<td>Para (4)-aminosalicylic acid</td>
<td>Imipramine</td>
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<tr>
<td>Penicillins</td>
<td>Isoniazid</td>
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<tr>
<td>Phenylbutazone</td>
<td>Loxoprofen</td>
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<tr>
<td>Piroxicam</td>
<td>Mephonacine</td>
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<tr>
<td>Pyrimethamine</td>
<td>Methotrexate</td>
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<tr>
<td>Sulindac</td>
<td>Methylphenidate</td>
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<tr>
<td>Sulfamides-sulfonamides</td>
<td>Nitrofurantoin</td>
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<tr>
<td>Tolfenamic acid</td>
<td>Nomifensine</td>
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<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>Pentamidine</td>
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<td></td>
<td>Perindopril</td>
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<td></td>
<td>Phenytoin</td>
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<td>Propranolol</td>
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<td></td>
<td>Sulfasalazine</td>
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<td></td>
<td>Trimipramine</td>
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<tr>
<td>Manifestation</td>
<td>Drugs</td>
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<td>-------------------------------------------------------------------------------</td>
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<tr>
<td>Generalised rash with or without fever</td>
<td>Any drug is a possibility</td>
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<tr>
<td>Interstitial nephritis with eosinophiluria</td>
<td>Mostly seen with antibiotics</td>
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<tr>
<td>Pulmonary infiltrates</td>
<td>Antibiotics, gold compounds, allopurinol</td>
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<tr>
<td>Pleuropulmonary manifestations</td>
<td>Nitrofurantoin, minocycline, naproxen, penicillins, phenylbutazone,</td>
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<tr>
<td>Hepatitis</td>
<td>sulindac, piroxicam, sulphonamides, nimesulide, tolfenamic acid</td>
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<tr>
<td>Leucocytoclastic vasculitis</td>
<td>Dantrolene sodium, bleomycin, methotrexate</td>
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<tr>
<td>Chronic rhinosinusitis with nasal polyposis and asthma</td>
<td>Phenothiazines, penicillins, tolbutamide, allopurinol, methotrexate,</td>
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<tr>
<td>Eosinophilia-myalgia syndrome</td>
<td>fluoroquinolones</td>
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<tr>
<td>DRESS syndrome (drug rash with eosinophilia and systemic symptoms)</td>
<td>Allopurinol, phenytoin</td>
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<td>Aspirin</td>
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<td>L-tryptophan</td>
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<td></td>
<td>Carbamazepine, allopurinol, antibiotics, etc.</td>
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</tbody>
</table>
• Eosinophilic- myalgia syndrome
• Toxic oil syndrome- dSSc like / spain 1981  Acute→ resp failure- death
Chronic→ HTN/SSc/hepatic/sicca/polyneuropathy/jt contractures/chronic pulmonary sequelae
• May resemble
  ICEP/IAEP/CSS
• Stop drugs
• Corticosteroids±
Bronchocentric granulomatosis

• inflammatory and destructive process beginning within the bronchiolar walls and further extending into the surrounding parenchyma with a peribronchiolar distribution of the lesions.
• 50% pt are asthmatics.
• Scattered fungal hyphae.
• blood eosinophilia >1000 eosinophils/mm³.
• **CXR** → The radiographic features consist of masses, alveolar opacities or pneumonic consolidation, or reticulonodular opacities, which predominate in the upper lobes and are u/l in majority.

• Most of these patients fulfill the criteria for ABPA.

• Corticosteroids are efficient with an excellent prognosis, although recurrences are common.
Initial workup

- Drug history
- Travel history?
- Serology testing for selective helminths
- 3 stool specimen & urine specimen for ova & larvae
- Asthma history
- PFT
- ANA/ANCA
- HIV
• Serial complete Hgm
• Serum IgE
• Vitamin B12
• ECG,ECHO
• HRCT thorax
• BAL
• Specific IgE,IgG
• Serum precipitins
Am J Respir Crit Care Med 150:1423–1438, 1994.)
<table>
<thead>
<tr>
<th>Normal (IU)</th>
<th>Mildly high (≤500 IU)</th>
<th>Moderately high (500–1000 IU)</th>
<th>Extremely high (&gt;1000 IU)</th>
</tr>
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<tbody>
<tr>
<td>Tuberculosis</td>
<td>Coccidioidomycosis</td>
<td>Strongyloidiasis</td>
<td>Allergic bronchopulmonary aspergillosis</td>
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<td>Brucellosis</td>
<td>Drug-induced</td>
<td>Schistosomiasis</td>
<td>Tropical pulmonary eosinophilia</td>
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<td>Hydatid cyst (encapsulated)</td>
<td>Loeffler’s syndrome</td>
<td>Paragonimiasis</td>
<td>Churg-Strauss syndrome</td>
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<td>Amebiasis</td>
<td>Sezary syndrome</td>
<td>Hydatid cyst (if cyst leaks)</td>
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<td>Polyarteritis nodosa</td>
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<tr>
<td>Langerhan’s cell granulomatosis</td>
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<tr>
<td>Sarcoidosis</td>
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