Eosinophilic syndromes

Mike Levin
Red Cross Allergy Clinic

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March 2012
Mast cells, basophils, eosinophils

Express many of the same receptors and cytokines but different effector functions

- **Mast cells:** Tissue resident
  Immediate hypersensitivity
  Preformed and newly synthesised mediators
  TNF alpha, IL3, IL5, IL13, GM-CSF, little IL4

- **Basophils:** Circulating
  Home to allergic inflammation
  Preformed and newly synthesised mediators
  IL4, IL13, GM CSF, little IL5

- **Eosinophils:** Resident in GI tract
  Home to allergic inflammation
  Effector function through granule proteins
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Eosinophils

• Multifunctional white blood cells
• About 1-3% of circulating leukocytes
• Range 0 to $0.5 \times 10^3$/mm$^3$
• Normally reside in mucosal tissues such as the GI tract (except for oesophagus)
• Key cell of allergic inflammation
• Organ morphogenesis
• Innate immune responses
Eosinophils

- Derived in bone marrow
- Enter the circulation as mature leukocytes
- Migrate to tissues
- Life span in blood: 24 hours
- Tissue : blood ratio of 100:1
Eosinophilic syndromes

Eosinophil Morphology

- Primary granules
- Distinctive bi-lobed nucleus
- Lipid bodies
- Scanty endoplasmic reticulum
- Charcot–Leyden crystals (only seen in cytoplasm during activation)
- Specific secondary granules

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• Secondary granules
• Nucleus
• Lipid bodies
• Primary granules

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Eosinophil basic proteins

- Major basic protein
- Eosinophil cationic protein
- Eosinophil peroxidase
- Eosinophil derived neurotoxin
Eosinophil basic proteins

• Major basic protein
  • Helminth parasites and bacteriocidal
  • Cytotoxic to airway epithelium
  • BHR
  • Activates basophils and mast cells
  • Platelet agonist
  • Activates complement

• Eosinophil cationic protein
• Eosinophil peroxidase
• Eosinophil derived neurotoxin

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Eosinophil basic proteins

• Major basic protein

• Eosinophil cationic protein
  • Weak ribonuclease (RNase) activity
  • Toxic to parasites and bacteria
  • Toxic to RNA pneumoviruses (incl RSV)
  • Cytotoxic to tumours and epithelium

• Eosinophil peroxidase

• Eosinophil derived neurotoxin
Eosinophil basic proteins

- Major basic protein
- Eosinophil cationic protein
- Eosinophil peroxidase
- Eosinophil derived neurotoxin
  - Strong RNAse activity
  - Weakly toxic to parasites
  - Toxic to RNA pneumoviruses (incl RSV)
  - Activates dendritic cells
  - TH2 polarisation
Eosinophil basic proteins

• Major basic protein
• Eosinophil cationic protein
• Eosinophil peroxidase
  • Toxic to mammalian cells by oxidising halides, pseudohalides and nitric oxide
  • Bacteriocidal
  • Cytotoxic to airway epithelium
• Eosinophil derived neurotoxin
Measuring ECP

- Also known as ribonuclease 3
- ECP is released during degranulation of eosinophils

- Monitoring eosinophilic inflammation
- Monitoring asthma “activity”
- Severity? Symptom onset?
- Correlates with eczema clinical score
## Lancet labs 2007-2011

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<td>33 520</td>
<td>33 641</td>
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<td>954 751</td>
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</table>

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Development

- Develop and mature in bone marrow
  - Differentiate from myeloid precursors in response to cytokines IL-5, IL-3, GM-CSF
  - Transcription factors GATA-1, PU.1, c/EBP
- Exit to circulation
- Home to GI tract, diseased tissues
- Do not return to blood

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Migration

Mechanisms regulated via IL 5, 4, 13 others
Migration and survival

• migrate to inflammatory sites
  • CCL11 (eotaxin-1), CCL24 (eotaxin-2)
  • CCL5 (RANTES)
  • leukotriene B4 (LTB4)

• Activated by Th2 cytokines IL-5, GM-CSF, and IL-3

• Eosinophils die by apoptosis or necrosis
  • IL-5, IL-3, GM-CSF, Ifn-γ prolong survival
  • IL-5, GM-CSF delay apoptosis, promote priming and activation
IL-5

- IL5 \(\rightarrow\) IL 5 receptor
- \(\beta_c\) subunit stimulation \(\rightarrow\) phosphorylation of tyrosine kinases, Jak2, Lyn, Syk
- A tyrosine kinase is an enzyme that can transfer a phosphate group from ATP to a protein in a cell
- It functions as an "on" or "off" switch in many cellular functions

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IL-5

• Tyrosine kinase stimulation of cellular function
  • Jak2 → STAT1 → transcription of nuclear factors to prevent apoptosis
  • Lyn, Syk → Ras-Raf1-MEK-ERK pathway → stimulates cell division via mitosis
• Proliferation of eosinophils

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Eosinophilia

- About 1-3% of circulating leukocytes
- Range 0 to $0.5 \times 10^3/mm^3$
- Diurnal variation: Low in am, high in pm
- 40% variation in counts throughout the day
- Mild: $0.5 to 1.5 \times 10^3/mm^3$
- Moderate: $1.5 to 5.0 \times 10^3/mm^3$
- Marked: $> 5.0 \times 10^3/mm^3$
Common causes

- Allergy: Eczema, Asthma, Rhinitis, Urticaria
- Parasite infestation: GI, lung, skin
- Drug allergies
- Allergic skin diseases
- Some forms of malignancy
- Systemic autoimmune diseases (e.g. SLE)
- Vasculitis (e.g. Churg-Strauss syndrome)
Hypereosinophilic syndrome

• Blood eosinophilia >15,000/mm³ for > 6 months (or death before 6 months)
• No parasite, allergic or other cause of eosinophilia
• Organ involvement
  • CVS
  • GIT
  • CNS
  • Systemic symptoms
Hypereosinophilic syndrome

• Very rare
• Mean age of presentation of 33 years
• Males (9:1)
  • Systemic symptoms: fatigue, pain, fever, night sweats and pruritus
  • GI: Diarrhoea, abdominal pain and nausea
  • CVS: Chest pain and breathlessness
  • Respiratory: shortness of breath, and dry cough.
Organ involvement

- Blood: thrombocytopenia, hypercoagulability
- Cardiac: CMO, valve abnormalities, pericardial effusion, thromboembolic disease
- Resp: pneumonitis, pulmonary emboli, pleural effusion, eosinophilic infiltrates
- CNS: CVA, confusion, ataxia, peripheral neuropathy
- GIT: Inflammation, infarction of the gut, splenomegaly, ascites, hepatitis, pancreatitis
- Skin: dermatitis, urticaria, papular rashes
- Eyes: episcleritis, retinal thrombi
- ENT: sinusitis

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Prognosis

- 5-year survival 80%
- Death from heart failure
- Treatment up till 2000: Steroids
Imatinib: Gleevec

- Treats chronic myeloid leukemia (CML), gastrointestinal stromal tumors and > ten other cancers
- May 2001: Gleevec receives FDA approval in fastest ever approval time
- May 2001: Cover of TIME magazine
- 2009: Manufacturers receive the Lasker-DeBakey Clinical Medical Research Award for "converting a fatal cancer into a manageable chronic condition"
- 2012: awarded the Japan Prize for their work
CML from pathology to cure

• 1960: Scientists at the University of Pennsylvania notice one chromosome in many CML patients was shorter than normal.
• The stubby chromosome was nicknamed “the Philadelphia chromosome”
• First time that a chromosomal defect was linked to cancer
CML from pathology to cure

- 1973: Researcher at the University of Chicago discovers the missing end of the short chromosome had moved and fused with another chromosome
CML from pathology to cure

- 1980s: Gene mapping shows that the broken chromosomes produce a cancer-causing protein
- 1986 and 1987: Researchers identify the protein as a tyrosine kinase
- Fusion between Abelson (Abl) tyrosine kinase gene at chromosome 9 and
- break point cluster (Bcr) gene at chromosome 22
- resulting in the chimeric oncogene Bcr-Abl
- and a constitutively active Bcr-Abl tyrosine kinase

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• Bcr-Abl changes the cell's normal genetic instructions, causing a constant signal to produce white blood cells.
• Gleevec blocks Bcr-Abl and “cures” CML without any toxic effect on other cells!
• Bcr-Abl has similar binding site to Src family kinases Lck and Lyn
HES: FIP1L1-PDGFRA

- PDGFRA is a type III tyrosine kinase
- Juxtaposition of FIP1L1 to PDGFRA → deregulated PDGFRA kinase activity
- FIP1L1-PDGFRA, a novel fusion gene on chromosome 4q1
- First description of a gain-of-function fusion gene from an interstitial chromosomal deletion rather than a reciprocal translocation
- Hypereosinophilic syndrome and chronic eosinophilic leukemia
Treatment of HES

- Imatinib mesylate: Gleevec
- High dose steroids
- Mepolizumab
- Hydroxyurea
- Interferon alpha
- Vicristine
- Cyclosporin
- PUVA therapy
Anti IL-5

- Among potential therapies for HES not responsive to imatinib, mepolizumab appears to be the most effective
- Humanized anti-IL-5 monoclonal antibody
- 95% had decreases in their eosinophil counts that yielded levels of less than 600/μL
- 87% of patients able to lower required steroid dose.
Tissue specific causes

- Lung
- Skin
- GIT
Tissue

• Lung
  • Asthma
  • Parasite infestation
  • Eosinophilic bronchitis
  • Eosinophilic pneumonia
  • Fungal colonisation
  • ABPA
  • COPD
  • Churg strauss
  • Ideopathic pulm fibrosis
  • Lung carcinoma

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Asthma

- Eosinophilic inflammation, mucus hypersecretion, and airway hyperresponsiveness
- Eosinophils a target for therapy
- Anti-IL-5 and anti-IL-13 monoclonal antibodies
- Anti-IL-5 ineffective in non-selected patients. Reductions in asthma exacerbations in those with sputum eosinophilia
ABPA

- Hypersensitivity to Aspergillus fumigatus
- Peripheral eosinophilia is common
- Dyspnoea
- Productive cough
- Wheezing
- Poorly controlled asthma despite maximal therapy
- Fleeting pulmonary infiltrates. Central bronchiectasis
## ABPA

<table>
<thead>
<tr>
<th>Asthma</th>
<th>Eosinophilia</th>
<th>Precipitating antibodies to <em>Aspergillus</em></th>
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</thead>
<tbody>
<tr>
<td>History of infiltrates on chest X-ray</td>
<td>Elevated total IgE</td>
<td>Increased serum IgE to <em>Aspergillus</em></td>
</tr>
<tr>
<td>Central bronchiectasis</td>
<td>Positive skin prick test to <em>Aspergillus</em></td>
<td></td>
</tr>
</tbody>
</table>

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ABPA

- Treatment with oral corticosteroids
- Many side effects
- Itraconazole for 6 months decreases total IgE, decreases eosinophil levels, and decreases need for prednisone
- No data on anti-IL-5 monoclonal antibodies or anti-IL-5 receptor therapies
Churg Strauss

- Autoimmune vasculitis with eosinophilia
- Refractory asthma
- Chronic sinusitis
- Transient pulmonary infiltrates and "pneumonia"
- Fatigue
- Weight loss
Churg Strauss

- Medium and small vessel vasculitis
- Purpura, urticarial type or maculopapular
- End organ damage
  - vasculitis in the small bowel, as well as eosinophilic inflammation of the GI tract
  - Peripheral neuropathy
  - CMO, pericarditis
Churg Strauss

- Associations: Montelukast and omalizumab?
- Treatment
  - Prednisone
  - Azathioprine
  - Methotrexate
  - IVIG
- Anti-IL-5 or anti-IL-5-receptor-α antibody
  - Decrease blood eosinophilia significantly
Eosinophilic pneumonias

- Rare disorders
- Acute or chronic eosinophilic pneumonia
- Pathophysiology largely unknown
- Galectin-9 (eosinophil chemoattractant) increased in BAL fluid
- Antibiotic use and smoking have been associated with its onset
- Acute eosinophilic pneumonia, patients respond to corticosteroids
Chronic eosinophilic pneumonia

- Fever, fatigue, cough, and pulmonary infiltrates
- CT: consolidation, ground-glass opacities or band-like subpleural opacities
- Middle aged; female > male
- BAL eosinophils
- Responds to prolonged therapy with prednisone
- Relapse common
Skin

• Eosinophils usually not present in the skin
  • Allergy: AD, urticaria, drug reactions (DRESS)
  • Infections: HIV, parasites, insect bites, erythema chronicum migrans
  • Autoimmune: Bullous pemphigoid, dermatitis herpetiformis
  • Erythema toxicum neonatorum
  • Hyper IgE syndrome
  • Eosinophilic cellulitis (Wells sy, hyper-eos sy)
  • Neoplasms (histiocytosis, chronic eosinophilic leukaemia, AML, CML, myelodysplasia, HES)
Skin disease

- Atopic dermatitis
- Urticaria
- Drug reactions
- Episodic angioedema
- Eosinophilic cellulitis (Wells syndrome).
Well’s syndrome

- Uncommon disorder that mimics cellulitis
  - Bright red at first
  - Fades over four to eight weeks
  - Leaving green, grey or brown patches
  - Can blister
  - Most commonly on the limbs
  - Also trunk

- Lethargy and fever in 25%

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Well’s syndrome

- Skin biopsy
  - significant eosinophilic infiltrate
  - presence of flame figures
  - no evidence of vasculitis

- Aetiology is unclear. Patients may have several episodes during their lifetime

- Oral steroids (Mild cases topical steroids)

- Other treatments include minocycline, dapsone, griseofulvin, ciclosporin and oral antihistamines
Drug reactions

• Drug rash with eosinophilia and systemic symptoms (DRESS)
• Uncommon but clinically important
• Delayed, type IV immune response
• Begins 1–8 weeks after initiation of the offending agent
• Antiepileptics and antimicrobials (tetracyclines and sulfonamides)
DRESS

- Rash
- Fever
- Lymphadenopathy
- Pharyngitis
- Fatigue
- 30% eosinophilia
- Hepatitis 50%, nephritis 30%
- Fatalities related to end organ damage

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RegiSCAR criteria. Three of the four starred criteria required for diagnosis

Japanese consensus group criteria. Seven criteria or the first five criteria (atypical)

Hospitalization

Reaction suspected to be drug-related

Acute Rash*

Fever > 38° C*

Lymphadenopathy in at least two sites*

Involvement of at least one internal organ*

Blood count abnormalities (lymphopenia or lymphocytosis*, eosinophilia*, thrombocytopenia*)

Maculopapular rash developing > 3 weeks after starting the suspected drug

Prolonged clinical symptoms 2 weeks after discontinuation

Fever > 38° C

Liver abnormalities (ALT > 100 U/L) or other organ involvement

Leukocyte abnormalities

Leukocytosis ( > 11 x 10⁹/L)

Atypical lymphocytosis (>5%)

Lymphadenopathy

Human herpesvirus 6 reactivation

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DRESS

- Human herpes virus 6 in a subset of patients
- Symptoms resolve with removal of the drug
- Supportive and symptomatic therapy
- Systemic corticosteroids
Eosinophilic renal disease

- Interstitial nephritis
- Fever
- Arthralgias
- Rash
- Renal failure
- Eosinophilia and eosinophiluria in small proportion but highly specific
Interstitial nephritis

• Medications
  • NSAIDs esp aspirin
  • Antibiotics such as penicillin and cephalexin, rifampicin, sulfa drugs, quinolones
  • Diuretics, allopurinol, and phenytoin

• Pyelonephritis
• Removal of the drug
• Corticosteroids are controversial
• Nutrition
• Supportive therapy
EGIDs

- Diverse collection of diseases
- Inappropriate accumulation of eosinophils in GI tract
- 25–50% of patients have eosinophilia
- Eosinophilic oesophagitis most common
- EoE diagnosis is on the rise
- Increasing recognition from increased endoscopy and biopsy
EGIDs

• GIT

  • Eosinophilic oesophagitis
    - Primary
    - Reflux
    - Eosinophilic gastroenteritis
    - Parasite infections
    - Connective tissue diseases eg scleroderma
    - Leiomyomatosis
    - HES

  • Eosinophilic gastroenteritis

  • Eosinophilic colitis
Eosinophilic Oesophagitis

- Male predilection, paediatric to adult populations
- Mean age in children ranges from 7-10 years, and 30-40 years in adults
- Adults: Longstanding dysphagia
  - Food impaction, reflux symptoms, vomiting
  - Food allergy 25%, atopy 46%
- Children
  - Abdominal pain 30%, vomiting 30% and failure to thrive 20%
  - Asthma 36.8%, rhinitis 57.4%, food allergy 46%, eczema
  - Family history of atopy 73.5%


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Eosinophilic Oesophagitis

- Eosinophilic infiltration of the squamous epithelium
  - >15/HPF
  - On adequate doses of anti reflux treatment
  - After control of allergic rhinitis

- Diagnostic sensitivity of 100% if 5 biopsies taken

- GERD can increase eosinophils <10/HPF

- Proximal vs distal pathology
  - Mid or upper oesophageal biopsies with increased eosinophils is more specific for eosinophilic oesophagitis

- Other features
  - Basal zone hyperplasia
  - Increased papillary size
  - Layering of eosinophils → aggregates or microabscesses
Eosinophilic Oesophagitis

- Skin prick tests and patch
- IgE only for associated immediate food hypersensitivity
- Dietary therapy: empiric / guided
- Anti-inflammatory therapy: Steroids
- Anti-IL-5: Substantial reduction in the number of eosinophils but little clinical resolution
- Anti-IL-13: Phase I clinical trials
EGIDs

• GIT
  • Eosinophilic oesophagitis
  • Eosinophilic gastroenteritis
    – Primary
    – Celiac
    – Connective tissue
    – Parasite infections
    – IBD
    – Churg Strauss
    – HES
  • Eosinophilic colitis
Eosinophilic gastroenteritis

- Presentation depends on
  - location
  - depth
  - extent of bowel wall involvement

- Chronic relapsing course

- mucosal, muscular and serosal types
Eosinophilic gastroenteritis

- **Mucosal**
  - vomiting, dyspepsia, abdominal pain, diarrhea, blood loss in the stools, iron deficiency anemia, malabsorption, protein-losing enteropathy, and failure to thrive.

- **Muscularis**
  - gastrointestinal obstructive symptoms mimicking pyloric stenosis or gastric outlet syndrome.

- **Serosal**
  - bloating, exudative ascites, and higher peripheral eosinophil counts.
Eosinophilic gastroenteritis

- Less likely to be food allergy related
- Elimination of foods has variable effects
- Supportive treatment
  - Oral steroids, entocort
  - Oral cromolyn
- Uncommonly respond to montelukast, ketotifen, suplatast tosilate, and mycophenolate mofetil
EGIDs

• GIT
  • Eosinophilic oesophagitis
  • Eosinophilic gastroenteritis
  • Eosinophilic colitis
    – Primary
    – Eosinophilic gastroenteritis
    – Celiac
    – Connective tissue
    – Parasite infections
    – IBD
    – Churg Strauss
    – HES

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Eosinophilic colitis

• Least frequent of EGIDs

• Acute self-limited bloody diarrhea in otherwise healthy infants
  • benign, frequently food-related

• Chronic relapsing colitis in young adults
  • Fever, diarrhoea, bloody stools, constipation, obstruction/strictures, acute abdominal pain, and tenderness
  • Aggressive medical management including: glucocorticoids, entocort, antihistamines, leukotriene receptors antagonists as well as anti IL-5 and anti IgE.
Immunodeficiency

- HIV
- Hyper Ig-E syndrome
- Omenn Syndrome
Ommenn syndrome

• Rare form of SCID
• Autosomal recessive mutations in the RAG1 and RAG2 genes
  • Altered VDJ recombination and impaired T- and B-cell maturation.
  • Absent to very low levels of circulating T and B cells
  • Low immunoglobulin levels
  • Immune dysregulation
  • Profound eosinophilia and lymphocytosis
Omenn syndrome

• Diagnosed in 1st 6 months
  • Severe eczema-like rash
  • Failure to thrive
  • Chronic diarrhoea
  • Lymphadenopathy
  • Recurrent infections

• Therapy
  • Treat infections, IVIG
  • Good nutrition, hydration
  • Correction of anaemia
  • Bone marrow transplantation
Parasites

• Most common cause of eosinophilia

• Helminthic parasites
  • Flatworms (flukes, tapeworms) and roundworms
  • Strongyloides (pinworm) infection can become invasive and fatal in patients treated with prednisone

• Dientomeba fragilis
  • travellers diarrhoea, chronic diarrhoea, fatigue and failure to thrive.

• Isopora belli
  • non-bloody diarrhea with crampy abdominal pain, which can last for weeks and result in malabsorption and weight loss.
Toxocara canis

• Dog roundworm
• Visceral larva migrans
• Migrating through the intestinal wall
• Travel through blood to organs
• liver, heart (myocarditis) and CNS (dysfunction, seizures, and coma)
• Eyes: ocular larva migrans
Eosinophils

- Important cells
- Many functions, not just worm defence
- Basic proteins major effector mechanism
- Develop, migrate and survive under control of IL-5
- Many common and uncommon causes of eosinophilia
- IL-5 and IL-5 related tyrosine kinase potential targets for new therapies