Well, it’s not Lupus!

Rheumatology Team
Case 1

- GP referral to Infectious Diseases
- IDDM
- Yoga teacher
- Persistent high white cell count
- Dry cough for several years-related to exertion
- Chest exam normal, peak flow 400
- Lived in Behar India for 12 years, returned last year
- ?Parasitosis
Clinic evaluation

- Dry cough
- Rural and urban areas, never hospitalised
- Since return worsening cough and malaise
- Occasional joint pain, no rash, occasional wheeze, no diarrhoea, vomiting, dysuria, eye symptoms
- Fhx of asthma, eczema. No pregnancies, no meds (monteluklast)
- Exam: unremarkable
- GP bloods: ESR 19, WCC 18, Eos 12.1, stool negative
• Schistosomiasis serology negative
• ID: Not infectious ?inflammatory disorder
Generalised myalgia, fatigue, dry cough, dyspnoea, wheeze
Symmetrical polyarthritis affecting shoulders, hips, thighs. EMS of 30 mins
Paraesthesia affecting initially left and now right foot for past 12 months
Exam: no synovitis
No rash
CVS/ Resp exam: normal
• No sensory abnormalities
• Decreased dorsiflexion right foot
• Urinanalysis normal
• HRCT: multiple nodules with upper lobe infiltrates
• Mild pericardial effusion
• Eosinophil count 8.4
• Moderately raised inflammatory markers
Investigations

- PFTs: FEV₁ 2.7 l, FEV₁/FVC 62%, lung volumes, RV/TLC normal. DLCOc 61% predicted

- BAL eosinophilia

- Histology: Eosinophilic infiltrate of the interstitium and intraalveolar space with some macrophages

- MDM discussion:
  - Most likely diagnosis, Churg Strauss or eosinophilic pneumonia with parasitic infestation unlikely.
NCS

- Subjective sensation of decreased movement in her feet and right foot flopping in front of her.
- Needle EMGS neuropathic features lower limbs
- Mild lumboscral polyradiculopathy
- Wide spread motor axonal polyneuropathy.
ACR Criteria

- Asthma
- Eosinophilia > 10% of differential
- History of allergy
- Mononeuropathy or polyneuropathy
- Pulmonary infiltrates, non fixed
- Sinous abnormalities
- Extra-vascular eosinophilia
Progress

- Commenced 1mg/kg prednisolone
- Azathioprine 150mg
- Over one year, commenced methotrexate
- CT nodularity and ground glass appearance resolved
- Serial ECHOs unremarkable
- Well maintained off steroids on methotrexate SC 15mg.
Case 2

- GP referral
- Urgent referral- ?Lupus
- Intermittent joint swelling (arms) ........11 years
- Attacks followed by blotchy rash
- “Vasculitic, urticarial” rash on skin, thighs, abdomen
- Significant malaise
- Antihistamines no benefit
- Recurrent presentations to ED- prednisolone helpful
• ANA and anti-dsDNA negative
• Complement C₃ 0.82, C₄ 0.08
• Alb 38
• Creat 92
Bloods

- WCC 12.36
- HB 13.8
- RBC 4.41
- HCT .43
- MCV 97.4
- PLT 250
- NEUTS 4.7
- EOS 5.39-10.8 (elevated)

- TPROT 100
- IgG 37
- IgA 5
- IgM 10
Rheum OPD

- Asthma, bronchitis
- Grommet insertions
- Smoker 5/day
- Symbicort inhaler
• 10 year history of intermittent swelling and rash affecting arms, thighs, abdomen
• Initial flares yearly, now monthly
• ?Asthma flares at same time
• No arthritis, synovitis, paresthesia, epistaxis, haematuria, hearing loss, sinus trouble, headaches, visual loss, chest pain, palpitations, no hemoptysis.
• No significant FHx
• No pregnancies, normal cycles
P/C

- Rash with oedema on arms and legs
  - Intermittent x 10 years
  - Lasting days at a time
  - Increasing frequency and severity x 6/12
  - ? wheeze
  - Spontaneous resolution; accelerated by corticosteroids
  - Exam: Normal
• Working differential in the clinic
• ?Churg strauss, ?Parasitic process
• ANCA sent
• Urinanalysis requested
• Advised to contact Rheum team, if symptoms worsen.
Day 1 Investigations

- WCC 35
  - Eosinophils 32
- Hb 12.6
- Plt 342
- ANCA negative

- Creatinine 57
- LFT N
- Alb 39
- LDH 312

- Urinalysis NAD
Differential Diagnosis

- Reactive hypereosinophilia
  - Parasitic infection
  - Vasculitis – CSS, GPA, SLE
  - Pulmonary eosinophilic disease
  - Non-myeloid malignancy
  - Rare

- Clonal hypereosinophilia
Labs

- ANCA –ve
- ANA –ve
- dsDNA –ve
- C3 1.1
- C4 <0.08
Derm consult

- Rt lower limb swelling, with weedy texture to skin
- Urticarial vasculitis
- ?panniculititic process
- C1 esterase levels, C1q levels
- BJP
- Hep screen skin biopsy arranged
- Serum tryptase
- Stool analysis
Skin Biopsy

- Superficial and deep peri-vascular and interstitial eosinophilic infiltrate with scattered mast cells

- Consistent with eosinophilic cellulitis (Wells syndrome) rt knee
• In view of chronicity of symptoms not an infectious cause
• ?churg-strauss
• No pulm infiltrates, U/A and ANCA negative
Radiology

- **US Axilla**: B/L axillary adenopathy, lymph nodes morphology abnormal, right axillary LN

- **US abdomen**: splenomegaly 13.3, no ascites

- **CT-TAP**: no convincing features of eosinophilic pneumonia, ? Scattered nodules with mild intraseptal thickening, ? viral or hypersensitivity, moderate axillary, mediastinal lymphadenopathy

- **ECHO**: Rheumatic moderate mitral stenosis, RVSP 40 mmhg, MVA1.45.

- **PFTs**: FEV/FVC 69%, DLCOc 70% (20.21),
• Episodic angioedema
• Urticaria
• Eosinophilia
• Decreased c4
Causes

Allergic disorders
• asthma and/or atopic disease
• allergic bronchopulmonary aspergillosis

Infectious diseases
• helminthic infection
• ectoparasite infestations (scabies, myiasis)
• protozoal infection
• fungal infection (especially coccidiomycosis)
• human immunodeficiency virus infection
Causes

Neoplasms
- leukaemia
- Lymphoma
- adenocarcinoma

Immunedysregulation
- Sarcoid
- IBD
- connective tissue disorders

Radiation exposure
Cholesterol embolisation
Lymph Node FNA

- Polymorphic lymphoid population with numerous eosinophils
  - No malignant cells
  - No granulomas

- c/w marked eosinophilia in a reactive lymph node
Lymphocyte sub-population analysis:
- T-cells 76% (helper 55%; suppressor 20%)
- NK cells 16%
- B cells 6%
- No aberrant T-cell populations
Genetics

- **FIP1L1-PDGFRA fusion gene absent**
  - 800kb deletion on 4q12 between 2 genes
  - FIP1L1 product plays role in mRNA processing
  - PDGFRA gene is an active kinase
  - Fusion gene present in variety of neoplastic hypereosinophilic disorders
Diagnosis?
Dx: Gleich Syndrome
Gleich Syndrome

- First described in 1984 - 2 children & 2 adults

- Recurrent attacks of angioedema, urticaria, and fever with marked eosinophilia

- Glucocorticoid responsive

- No vital organ involvement (f/u 2 - 17 years)

syndrome of episodic angioedema associated with eosinophilia

is characterized by cyclical attacks of weight gain associated with urticaria, fever and marked eosinophilia often on a regular basis

Eosinophil counts reach as high as 95 · 10^9/l. In most cases, IgM is increased and IgG and IgE may be increased.

(Gleich et al, 1984).
• IL-5 readily detectable in serum during attacks.

• during the evolution of an attack showed that IL-5 peaks 4 d and eosinophils 2 d before the maximal weight

Butterfield et al, 1992
Gleich Syndrome

- Several cases worldwide
  - $M = F$
  - 2-40 years

- Cyclical; 22 day cycle reported by some
TH-2 driven process with loss of TH-1 / TH-2 equilibrium

- IL-5
- eosinophil activation
- major basic protein
- basogenic oedema
T cell clones, especially CD3−D4+, are present in some patients.
syndrome of nodules, eosinophilia, rheumatism, dermatitis and swelling (NERDS) present with large, compressible nodules arising from the tenosynovium of the extensor tendons and recurrent attacks of angioedema

Less episodic in Asian populations (Chikama et al)

Recurrent facial oedema show marked eosinophilia with deposition of major basic protein in the affected tissues the oedema is responsive to treatment with prednisone.
Prognosis

- Benign but often incapacitating disease

- Unlike other eosinophilic disorders, no vital organ involvement
  - eosinophilic gastroenteritis
  - endomyocardial fibroelastosis
  - eosinophilic pneumonia
HES

- proposed by Hardy and Anderson (1968)

- three male patients with marked peripheral blood eosinophilia who developed severe cardiac disease

- HES presents with blood, heart, nervous system, lung and, especially, skin involvement

- Presence of splinter hemorrhages
Diagnostic Criteria

- In 1975, Chusid et al established the following set of diagnostic criteria for idiopathic HES:
  - i) blood eosinophilia $> 1500/\text{mm}^3$ for at least 6 months,
  - ii) absence of an underlying cause of eosinophilia despite extensive evaluation
  - iii) presence of end organ damage or dysfunction related to the eosinophilia
Proposed Work up

- complete history and physical examination, a complete blood count and differential

- routine chemistries, serum IgE and vitamin B₁₂ levels, HIV serology, tryptase, electrocardiogram, echocardiogram, pulmonary function tests, chest and abdominal CT, and bone marrow aspirate and biopsy.

- Cytogenetics for chromosomal abnormalities to include *FIP1L1-PDGFRA* deletional mutation T cell subsets for clonality by cytoflow/T cell receptor gene rearrangement B cell clonality analyses

- organ-specific evaluations and biopsies for eosinophilic granular proteins

- Testing for occult parasitic infection with stool examination for ova and parasites and/or specific serologic tests
Back to Case...

- Upon confirmation of diagnosis
  - prednisolone 30mg od tapering

- Rapid resolution of rash & symptoms, advised to monitor signs and symptoms

- Weight record

- IL-5 levels
  - 66ng/l → 35ng/l → <5ng/l within 5 days
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**Eosinophils**

The graph shows the number of eosinophils per liter of blood, measured in millions ($x10^9/l$), over a period from Wed 15 to Fri 24. The values are marked with blue circles on the graph. The data indicates a trend where the eosinophil count increased from Wed 15 to Thu 16, reached a peak on Fri 17, and then decreased significantly from Sat 18 onwards.
Future Management

- Anti-IL5 therapy as potential steroid-sparing agent in future
- Mepolizumab – humanised anti-IL5 monoclonal antibody
- Recent Eos count 2.49
Exclusion of secondary causes

morphologic review of the blood and marrow, standard cytogenetics, fluorescent in situ-hybridization, flow immunocytometry, and T-cell clonality assessment

To detect histopathologic or clonal evidence for an acute or chronic myeloid lymphoproliferative disorder.
Conclusion

- WHO scheme of disease subtypes including, myeloid and lymphoid neoplasms with eosinophilia
- abnormalities of PDGFRA, PDGFRB, or FGFR1
- idiopathic hypereosinophilic syndrome (HES), which is a diagnosis of exclusion.
Conclusion

- Milder forms of eosinophilia (e.g., <1,500/mm³) without symptoms or signs of organ involvement, a watch and wait approach with close-follow-up may be undertaken.

- Identification of rearranged PDGFRα or PDGFRβ is critical because of the exquisite responsiveness of these diseases to imatinib.
• Corticosteroids are first-line therapy for patients with lymphocyte-variant hypereosinophilia and HES.

• Although clinical trials have been performed with anti IL-5 (mepolizumab) and anti-CD52 (alemtuzumab) antibodies, their therapeutic role in primary eosinophilic diseases and HES has yet to be established.
Asthma, History of allergy

Eosinophilia > 10% of differential

Mononeuropathy or polyneuropathy

Pulmonary infiltrates, non fixed

Sinus abnormalities

Extra-vascular eosinophilia
Thank You