Combined Rheumatology Meet

Hospital Selayang
28 JAN 2005
YCW 34 yr old Chinese male

- Deaf mute ( ? febrile illness in infancy )
- Referred from HKL in Feb 2001
  - hx of digital gangrene a/w Raynaud’s
  - no symptoms to suggest CTD
  - no dry mouth or eyes
  - no oral / genital ulcers
  - no joint pain or swelling
  - no constitutional complaints
  - no calf claudication
  - no amaurosis fugax / syncope / seizures
- long standing dry pruritic skin
- no known medical / surgical illness
- FHx – parents hypertensive, nil others
- single, lives with parents
- unemployed - helps sister occasionally in pasar malam
- does not smoke / consume alcohol
- allergic to ticlopidine
- systems review - NAD
Physical examination

- pink, not jaundiced
- BP not measurable
- Lungs clear
- CVS DRNM
- Abdomen – no hepatosplenomegaly, no renal bruit
- CNS NAD
- no carotid bruit
Physical examination

- xerotic lichenified skin; papulonodular pruritic lesions
- atrophied finger pulps, digital scars
- dry gangrene of R thumb & L middle finger
- FFD L middle finger with distal resorption
- ray amputation of 1\textsuperscript{st} and 2\textsuperscript{nd} toes R foot
## Physical examination

<table>
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<tr>
<th>Pulses</th>
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<td>Carotid</td>
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<td>Brachial</td>
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<td>Radial</td>
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<td>Femoral</td>
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<td>Dorsalis pedis</td>
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<td>Post tibialis</td>
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Physical examination

- multiple R axillary LN: 1x1cm, rubbery, mobile, non tender
- L axillary LN: 2x2cm, mobile, non tender
- small inguinal LN 0.5 – 1cm diameter
- no cervical LN
- fundoscopy – bilateral tilting discs with R eccentric pupil
- auroscopy - NAD
Investigations

- FBC - eosinophilia, otherwise N
- RP / LFT – N  Ca++ 2.45
- ESR – 12  CRP < 0.4
- FBS / FSL - N
- LDH - 241
- UFEME – NAD
- Stool ova & cyst – NAD
- Echo - NAD
Investigations

- ANA – reactive (speckled)
- Anti Sm – negative
- Anti RNP positive
- Anti Scl-70 negative
- Rh factor negative
- Anti SSA / SSB – negative
Investigations

- ANCA – negative
- HBsAg / HCV / HIV - non reactive
- ACL Ab – positive (low titre)
- VDRL - negative
- CXR normal
- L axillary LN biopsy (May 2003) – reactive changes
Normal calibre of both arteries and distal abdominal aorta before bifurcation. No areas of narrowing seen.

Both common iliac arteries normal. 30% narrowing of proximal right SFA. Left SFA normal calibre. Both profunda arteries normal.

Total occlusion of distal right SFA with collateral reconstitution via geniculate collaterals around knee joint. 40% narrowing of distal left SFA.

Total occlusion of left popliteal artery with collateral reconstitution at trifurcation.

Both plantar arches not opacified.
Arch / Abdominal Aortogram (Oct 2002)

- Normal arch of aorta
- **Non opacification of left axillary artery**. Presence of collaterals.
- Left subclavian artery normal.
- Brachiocephalic artery, right subclavian artery, right axillary artery and both carotid arteries normal
- Renal and mesenteric arteries normal
CT Thorax ( Aug 2003 )

- Multiple rim enhancing L axillary LN 0.5-3.5 cm, slightly indenting / compressing onto adjacent L axillary vein
- Round hyperdense lesion in R lower lobe - ? granuloma. L lung field clear
- No hilar or mediastinal nodes
- Enlarged liver with focal fatty change
Provisional diagnosis:
- ? Takayasu’s arteritis
- Hypereosinophilia 2° eczema

ACR criteria for Takayasu’s Arteritis (3/6)
1. **age onset < 40 years**
2. claudication of extremities
3. **decreased pulsation one / both brachial arteries**
4. SBP difference > 10 between arms
5. bruit in one / both subclavian arteries / abdominal aorta
6. arteriographic narrowing / occlusion of aorta, branches, large arteries
Management

- Started on Prednisolone in HKL ( ? initial dose )
- Continued on Prednisolone 10 mg OD
- Others: Pentoxyphylline 400 mg tds
  Aspirin 75 mg OD
  Amlodipine 2.5 mg OD
Progress

- 2001 – Aug 2004: remained stable
- Raynaud’s less severe
- No new ulcers / skin lesions
- Prednisolone tapered to 2.5 mg OD
- Persistent Eo – transient reduction after antihelminthiic
- Mother not keen for BMAT and repeat LN biopsy as patient well
Then

- Oct 2004, developed spontaneous painful periungual ulcers over both index fingers – minimal slough, no discharge
- Axillary LN not increased in size
- Few new erythematous pruritic lesions over nape of neck and forearm
- Pulses - status quo
- Examination otherwise unremarkable
More history

- Not significantly different from initial presentation
- No asthmatic / respiratory complaints
- No passage of worms in stool (repeated stool sample for ova and cyst negative)
- No pets
- No exposure to chemicals
- No OTC drugs / alternative therapy
Blood results

- Hb 14.0 g/dL
- Plt 180 – 200 x 10⁹
- Wbc 8.0 – 13.4 x 10⁹
- % Eo : 20.6 – 38.4 (N 0 – 5)
- abs Eo : 1.5 - 4.4 (N 0.4 -2.1)
More Investigations …..

- **Skin biopsy** - upper dermis shows mild to moderate perivascular infiltrate of lymphoplasmocytic cells and histiocytes, but no eosinophils noted
- **LN biopsy** – no granuloma or evidence of malignancy
- **BMAT** – normocellular with hyperEo, no morphological abnormalities
More Investigations ..... 

- repeat ACL / LAC – negative
- Protein C / S – normal
- Other factor deficiencies – to be checked
- Immunophenotyping – not sugg of PNH
- Ig M – normal       IgE – no results
- B12 – 658 g/L ( normal )
- LAP score – 75% ( normal )
Problems:
- persistent eosinophilia with no apparent cause, a/w
- Raynaud’s phenomenon
- digital ulcer and gangrene

?? differential diagnoses
DISCUSSION
? Diagnosis

➔ ? eosinophilic vasculitis a/w CTD

➔ ? cutaneous necrotising eosinophilic vasculitis

➔ ? idiopathic hypereosinophilic syndrome
- **Eosinophilic vasculitis a/w CTD**
  
  HPE: Eo predominate, but along with neutrophils and other inflammatory cells.

- **Cutaneous necrotising eosinophilic vasculitis**
  
  HPE: Eosinophils exclusively.
Management

- Pred increased to 50 mg OD (1 mg/kg)
- Colchicine 0.6 mg bd
- continued with aspirin, pentoxyphylline, amlodipine & hydroxyzine
- Eo count reduced significantly (5.6% or 0.8) at 2 weeks, normalised (4.4% or 0.6) at 6 weeks
- now on tapering dose of pred
Categories of eosinophilia

- Reactive (non-clonal):
  - infections, parasitic infestations
  - asthma and allergies, respiratory diseases
  - cytokine infusions
  - drug reactions
  - vasculitides, connective tissue diseases
  - non-haematological malignant diseases
  - Hodgkin’s and NHL
Categories of eosinophilia

- **Clonal disorders a/w Eo**
  - Acute and chronic Eo leukemia
  - AML and CML
  - PRV, Essential thrombocythaemia
  - ALL
  - MDS with eosinophilia
  - Systemic mastocytosis

- **Idiopathic Hypereosinophilic Synd**
Idiopathic Hypereosinophilic Syndrome (HES)

- Blood Eo count persistently $> 1.5 \times 10^9$/L (normally 0.1 - 0.6 $\times 10^9$/L) for $> 6/12$
- Damage to end organs eg heart, lungs, skin, joints and nervous system
- Absence of any clonal abnormality or reactive cause for eosinophilia
Pathophysiology

- eosinophilopoietin cytokines – IL-5, IL-3, G-CSF
- toxicity related to fibrosis caused by Eo granules, TNF-α, IL-1α, IL-6, IL-8 etc
- + urokinase-induced plasminogen & FXII-dependent rxn predispose to thrombosis
- major basic protein & Eo peroxidase potent stimuli of platelet activation and aggregation
Demographics

- incidence low
- race
  - 78% Caucasians
  - 18% Afro-Americans
  - 4% Asian Americans
- gender – 90% male predominance
- age – most common 40-50 y.o
Course of disease

- varies from asymptomatic to life-threatening multisystem disease
- death generally from $1^\circ$ heart damage or $2^\circ$ endocarditis
- survival prolonged if sequelae of organ damage esp cardiac, controlled
- mean survival 9 months
- 3-year survival rate ~ 12%
Poor prognostic factors

- anaemia
- thrombocytopenia
- WBC > $100 \times 10^9$ /L
- abnormal circulating basophilic cells
- abnormal bone marrow
- elevated vitamin B12 level
- abnormal LAP score
Clinical features

- **Constitutional** – fever, night sweats, anorexia, weight loss, fatigue
- **Heart** – arrhythmia, constr pericarditis, fibroblastic endocarditis, endomyocardial fibrosis, myocarditis, intramural thrombosis
- **Vascular** – Raynaud’s, thrombosis
- **PNS** – mononeuritis multiplex, peripheral neuropathy
Clinical features

- **CNS** – paraparesis, cerebellar involv, subacute encephalopathy, epilepsy, cerebral infarct and dementia, bilateral papilloedema, eosinophilic meningitis
- **Lungs** - pulm infiltrates and fibrosis, pleural effusions, pulmonary emboli
- **Joints** – arthralgia, effusions, destructive joint lesions, bursitis, polyarthritis
Clinical features

- **Skin** – angioedema, urticaria, digital necrosis, papulonodular, erythematous indurated plaques, vesicobullous lesions, recurrent incapacitating mucosal ulceration

- **GIT** – ascites, diarrhoea, gastritis, colitis, pancreatitis, cholangitis, hepatitis
Laboratory studies

- FBC – Eo > $1.5 \times 10^9$ /L
- ESR usually elevated (can be N)
- LAP high or low
- high Ig E in 33%
- rarely Ig G, A and M raised
- RF only rarely present
Laboratory studies

- Coombs may be +ve
- hematuria, proteinuria and azotemia
- synovial fluid Eo prominent
- chromosomal analysis
  - if abnormalities detected, work up for Eo leukemia
Other tests

- imaging studies
- ECG ( + ve findings in 90% )
- echocardiogram
- bone marrow
- tissue biopsy
Management

- Determine cause
- Evidence of end-organ damage
- Persistent eosinophilia
- Treatment: aim to lower Eo count and improve symptoms produced by end-organ damage
Medical therapy

- none indicated in absence of organ damage
- angioedema and urticaria suggests benign course
- mucosal ulcers no response to steroids
- rapid intervention essential for cardiac disease
- goal of Rx - reduce Eo load
- prevent thrombosis
Treatment

- Prednisolone 1 mg/kg/d
  - reduce Eo infiltration, effects of release of Eo granule contents, blood eosinophilia and suppress inflammation
  - response to steroid good prognostic indicator

- Cyclosporin - decrease T-cell production

- Hydroxyurea 1-2 g/d in steroid resistance

- Dapsone – anti-inflammatory, esp useful for skin involvement
Treatment

- Others – vincristine, chlorambucil, etoposide
  (restrict use as a/w risk of MDS and $2^0$ leukemia)
- New – IFN-α, STI 571, allogeneic stem cell transplantation
- Anticoagulant and antiplatelet agents
Skin biopsy (11/09/04)

- Focal basal cell degeneration a/w pigment incontinence. Occasional civatte bodies within epidermis
- Upper dermis shows mild to moderate perivascular infiltrate, composed of lymphoplasmocytic cells and histiocytes
- No eosinophils noted
- Consistent with erythema dyschroicmicum perstan (ashy dermatoses)
BMAT (27/10/04)

- **Cellularity**: fragment – normocellular
  - Cell trail – normocellular
  - Blasts – 1%
  - Myelocytes + metamyelocytes – 10%
  - Neutrophils – 42%
  - Erythroid precursors – 27%
  - Lymphocytes – 6%
  - Eosinophils – 15%

- **Erythropoiesis**: present with normoblastic maturation, predominant cells late normoblast

- **Leucopoiesis**: present with increased eosinophils. Some myelocytes show eosinophilic cytoplasm. All stages maturation present

- **Megakaryocytes**: adequate

- **Perl’s stain**: iron store adequate
Classification of vasculitides

- **Primary idiopathic vasculitis**
  - **Small vessel**
    - Wegener’s granulomatosis
    - Churg-Strauss syndrome
    - Microscopic polyangiitis
    - Idiopathic pauci-immune GN
    - Idiopathic capillaritis
Classification of vasculitides

- **Medium vessel**
  - Polyarteritis nodosa
  - Kawasaki disease

- **Large vessel**
  - Takayasu arteritis
  - Giant-cell arteritis
Classification of vasculitides

- **Primary immune-complex mediated vasculitis**
  - Goodpasture syndrome
  - Henoch-Schonlein purpura
  - IgA nephropathy
Classification of vasculitides

- **Secondary vasculitis**
  - SLE, RA
  - Polymyositis/dermatomyositis
  - Scleroderma
  - APLS
  - Inflammatory bowel disease
  - Hypocomplementemic urticarial vasculitis
  - Essential cryoglobulinemia
  - Drug-induced vasculitis
  - Paraneoplastic
Takayasu’s arteritis

- Type I: aortic arches and branches (10%)
- Type II: atypical coarctation of aorta i.e. involving thoracic descending and abdominal aorta (10%)
- Type III: mixed variety involving types I and II (65%)