Anti-Neutrophil Cytoplasm Antibody Associated Vasculitis

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VASCULITIS

- Inflammation of blood vessels.
- Classified according to the smallest vessel involved.
- Wegener’s Granulomatosis and Microscopic Polyangiitis associated with ANCA
Target Organs of Small Vessel Vasculitis

- Uncommon Disease
- Mainly affect the elderly.
- 20 patients /million /year
- Airway and renal organs most commonly involved.
- Can cause life threatening acute or chronic organ damage.
Lung Involvement

Normal Chest X-Ray

Pulmonary Vasculitis
Renal Involvement

Normal Glomerulus

Renal Vasculitis
Clinical Presentation

- Usually unwell for weeks/months before seeing doctor.
- Fever/Malaise/Anorexia/Weight loss
- Myalgia/Arthralgia
- Rash
- Sinusitis/Epistaxis/Hoarse voice
- Breathless/Haemoptysis
- Renal failure
- Abdominal pain/Diarrhoea
- Neuropathy
Diagnosis of Vasculitis

- Clinical suspicion
- No absolute diagnostic criteria.
- Lab Markers
  - +ANCA
  - High CRP
  - High ESR
  - High White cell and neutrophil count
  - High urea/creatinine

**ACR Criteria**
- Presence of 2 or more from … gives sensitivity of 88.2%, specificity of 92%
  - nasal/oral inflammation
  - abnormal Cxr
  - active urinary sediment
  - granuloma on biopsy
Differential Diagnoses

- Henoch-Schoenlein Purpura
- Anti-Glomerular basement membrane antibody disease
- Malignancy
- Infection
- Sarcoidosis
- Drugs (anti-thyroid, cocaine etc)
- Many others
Anti-Neutrophil Cytoplasm Antibodies

- Detected by indirect immunofluorescence and ELISA
- Directed against MPO (pANCA) or PR3 (cANCA)
- cANCA + PR3 specific for WG
- pANCA + MPO specific for MPA
- IIF or ELISA alone less specific
Pathogenesis of Vasculitis

- ANCA probably pathogenic though cause unknown.
- Seasonal variation.
- Association with S. Aureus infection.
- Production of IgG antibodies implies T-cell driven B-cell proliferation.
- Activated T and B-cells found in peripheral blood and tissues in active disease.
- Circulating and local pro-inflammatory cytokines – prime and activate leukocytes
Neutrophil Endothelium interaction

- ANCA bind to neutrophils
- Neutrophils adhere to endothelium.
- Neutrophils undergo respiratory burst.
- Endothelial and tissue damage ensues.
Mechanisms of endothelial cell damage in ANCA-associated vasculitis

- Primed PMN Activated by ANCA and adhesion to EC promoted
- Releases granule contents, H$_2$O$_2$ & NO leading to EC damage
- MPO causes EC detachment
- PR3 can cause EC apoptosis
- Necrotic PMN cause further EC damage

- Cytokine release causing EC activation, up regulation of adhesion molecules and affecting transmigration
- ANCA binds to surface antigen and promotes EC damage
- AECA cause further EC activation
- Opsonised apoptotic PMN phagocytosed by macrophage and pro-inflammatory cytokines released perpetuating inflammatory response

EC: Endothelial cell
AECA: Antiendothelial cell antibodies
PMN: Polymorphonuclear cell
MPO: Myeloperoxidase
PR3: Proteinase 3
Neutrophils Rolling
Neutrophils rolling with ANCA
Opsonised neutrophil fragments taken up by macrophages lead to further pro-inflammatory cytokine release and leukocyte recruitment.
Outcomes

- Untreated 80% mortality at 1 year.
- Treatment leads to 76% 5 year survival.
- Majority of deaths from infection, renal failure and pulmonary haemorrhage
- Worse outcome with:
  - Increased age
  - Renal Failure
Treatment

**Immunosuppression**
- Plasma exchange
- Corticosteroids
  - High dose tapers down
  - For 3 months then convert to…
- Cyclophosphamide
  - Continue for at least 1 year post remission.
- Azathioprine

**Side Effects**
- Diabetes
- Hypertension
- Infection
- Osteoporosis
- Neutropenia
- Malignancy (esp. bladder, lymphoma, leukaemia)
New Treatments

- TNF blockade – Infliximab/Etanercept
- Anti-B-Cell – Rituximab
- Anti-T-cell activation – CTLA-4
- Immunosuppressive – Deoxyspergualine
Infliximab

- Chimeric mouse/human antibody against TNFα.
- Developed for use in rheumatoid arthritis.
- Useful in Crohn’s disease and others.
- May be useful in vasculitis
- 4 doses over 10 weeks with steroids and cyclophosphamide.
Disease activity

Birmingham Vasculitis Activity Score vs Week

C Reactive Protein vs Week

Control vs Infliximab
Infliximab reduces neutrophil respiratory burst

Error Bars show Mean +/- 1.0 SE
Dot/Lines show Means

Ratio control\(\rightarrow\)bMLP induced respiratory burst

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Lymphocyte activation not affected by infliximab
Rituximab

- Mouse/Human chimeric Monoclonal Anti-CD20 antibody.
- Used in lymphoma therapy.
- Now being used in auto-immune diseases to reduce auto-antibody production
Figure 1: Plot of blood B cell count, PR3 titre, and total immunoglobulin levels, during Rituxumab therapy.
Research into Vasculitis at Birmingham University

- Nephrology
- Rheumatology
- Immunology
- Rheology

- Clinical trials into new therapies
- Lab research into mechanisms of
  - Neutrophil activation
  - ANCA production
  - T-cell involvement
  - Leukocyte-endothelial interaction
Summary

• Uncommon autoimmune inflammatory disease of older people.
• Causes life-threatening acute and chronic disease.
• May be difficult to diagnose.
• Treatment saves lives ……but may have severe side effects.