Clinical aspects of Autoantibodies in Rheumatology

Lee-Suan Teh
Consultant Rheumatologist
Royal Blackburn Hospital
Objectives

- Able to define autoantibodies
- Appreciate the associations between these antibodies and different rheumatological diseases
- Realise that knowledge is limited regarding these areas:
  - Why are they produced?
  - What are their clinical significance?
- Stepping stone for your future reading and understanding of autoantibodies

L S Teh 2010
Outline of talk

- What is an autoantibody? (AuAb)
  - How autoantibodies are produced

- Some common autoantibodies in Rheumatology
  - Rheumatoid factor (RF)
  - Anti-cyclic citrullinated peptide (CCP) Ab
  - Antinuclear factor (ANF, ANA)
    - Double-stranded DNA (single stranded DNA) dsDNA (ssDNA)
    - Extractable nuclear Ab (ENA)
    - Toisomerase (Scl-70)
    - Centromere
    - Jo-1
  - Phospholipid Ab (APA) and Lupus Anticoagulant
  - Antineutrophil cytoplasmic Ab (ANCA)

- Clinical associations of these antibodies
What is an autoantibody?

- “Auto” means “self” in Greek
- Autoantibodies are antibodies directed against self proteins

![Diagram of antibody structure with Fc and Fab portions]
Facts about autoantibodies

- For reasons still unclear, the body produces antibodies against its own antigens.
- Not all autoantibodies are pathogenic.
- May run in families.
- Not clear still if asymptomatic patients with autoantibodies will go on to develop disease.
Rheumatoid factor

- Antibody directed against Fc portion of IgG
- Is not diagnostic of Rheumatoid arthritis
- Can be seen in other diseases where there is polyclonal stimulation of B cells
- Does not follow clinical disease activity

- Usually IgM against Fc of IgG
- Can be IgG/IgG, IgA/IgG

L S Teh 2010
Detection of RF

- Rheumatoid latex test
- Rheumatoid arthritis particle agglutination test (RAPA)

- Occurs in Normals especially those over 50

- Diseases associated with RF
  - RA (25% of patients with RF have RA, 20% of patients with RA are negative for RF)
  - CTD (SLE, Sjogren’s syndrome, scleroderma)
  - Infections (TB, viral, syphilis, bacterial endocarditis)
  - Hepatitis
  - Sarcoidosis
  - Malignancy (leukaemia)
Anti-CCP antibodies

- Anti-cyclic citrullinated peptide antibodies
- More specific for RA
- More sensitive in early RA
- May predict a more severe erosive disease
- May predict a better response to certain DMARDs (esp Methotrexate) and biologics

L S Teh 2010
Antinuclear antibodies (ANA)

- Detected by immunofluorescence
- Have different patterns:
  - Diffuse
  - Speckled
  - Centromere
  - Nucleolar
- Have various specificities:
  - dsDNA, ssDNA
  - centromere
  - RNA (ENA)
    - Ro/SSA, La/SSB, RNP, Sm

LS Teh 2010
Clinical significance of ANA

- Diffuse pattern ANA
  - Nucleosomes
  - dsDNA, ssDNA
  - RA, SLE, drug-induced SLE

- Centromere pattern
  - limited cutaneous systemic sclerosis
  - Pulmonary hypertension

- Nucleolar pattern
  - Scl-70, fibrillarin, PM-Scl
  - Diffuse cutaneous systemic sclerosis, polymyositis-scleroderma overlap

- Peripheral (rim)
  - dsRNA,
  - SLE

- Speckled pattern
  - ENA (RNP, Sm, Ro/SSA, La/SSB)
  - MCTD/overlap syndrome
  - SLE, Scleroderma, EB, Sjogren’s syndrome
  - Infectious mononucleosis
  - Normals
ANCA

Cytoplasmic (cANCA)

- Antigens
  - PR3, rarely MPO

- Associations
  - Vasculitis
    - Wegener’s granulomatosis 90%
    - Microscopic polyangitis 40%
    - Rarely Churg-Strauss

Peripheral (pANCA)

- Antigens
  - MPO, lactoferrin, elastase

- Associations
  - Vasculitis
    - Microscopic polyangitis 60%
    - Churg-Strauss 40%
    - Polyarteritis rare
  - CTD (SLE, RA, Sjogren’s)
  - Chronic inflammatory bowel
  - Liver disease

L S Teh 2010
Antiphospholipid antibodies (aPL)

What are they?
- aPL are directed against **phospholipids** or **phospholipid-binding proteins**
  - Phospholipids include
    - Cardiolipin
    - Phosphatidylserine, phosphatidylinositol, phosphatidic acid, phosphatidylglycerol
  - Phospholipid-binding proteins
    - $\beta_2$-glycoprotein-1 ($\beta_2$-GP1)
    - Prothrombin
    - Annexin V

How are they detected?
- Enzyme-linked immunosorbent assay (ELISA)
  - Cardiolipin
  - $B_2$-Glycoprotein-1
- Lupus anticoagulant (LA) test
  - Phospholipid-dependent clotting tests
    - activated partial thromboplastin time (APPT)
    - dilute Russell viper venom test (dRVVT)
    - kaolin clotting time (KCT)
- 20% of patients with APS can be negative for one or other of tests

L S Teh 2010
## Prevalence of aPL

### Normal Individuals

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous Thrombosis</td>
<td>3-17%</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>5-15%</td>
</tr>
<tr>
<td>Recurrent Strokes</td>
<td>5-46%</td>
</tr>
<tr>
<td>SLE</td>
<td>20-40%</td>
</tr>
<tr>
<td>Infection (HIV, hepatitis, CMV, syphilis, leprosy)</td>
<td>N/K</td>
</tr>
<tr>
<td>Drug-induced (cocaine, hydralazine, procainamide, quinine)</td>
<td>N/K</td>
</tr>
</tbody>
</table>

- Age – young and middle-aged
- Sex – female predominance
- Race – vascular thrombosis alone more common in whites, pregnancy morbidity alone in non-whites

L S Teh 2010
Systemic Lupus Erythematosus (SLE)

- Mainly affects young women
  - Female:Male ratio of 9:1
  - More common in Afro-Caribbeans, Hispanics, South Asians, Chinese
  - 40 to 100/100,000

- Different types
  - Discoid Lupus
  - Systemic Lupus
  - Neonatal Lupus
  - Drug-induced

- Typical auto-antibodies
  - Antinuclear antibodies (ANA, ANF) – 98%
  - Double-stranded and Single-stranded DNA (dsDNA, ssDNA) - 70%
  - Ro/SSA 30% and La/SSB 15-20%
  - Antiphospholipids (anticardiolipin) 20%
  - Sm 30%
  - Ribosomal P 10-15%

- Non-specific features
  - Anorexia, Weight loss, fevers, fatigue, night sweats

LS Teh 2010
Visible Manifestations of Lupus

- Butterfly malar rash
- Discoid Lupus
- Alopecia
- Vitiligo and discoid rash
- Vasculitis and gangrene
Skin and Antiphospholipid Syndrome (APS)
(Vascular thrombosis, recurrent foetal loss, thrombocytopenia)

- Livedo reticularis
- Digital gangrene
- Splinter haemorrhages
Medical Management of SLE

- Depends on symptoms and organ involvement
  - Skin – topical, anti-malarials (hydroxychloroquine, mepacrine), steroids
  - Arthralgia/Arthritis
    - Non-steroidal anti-inflammatory drugs (NSAIDs – Ibuprofen, diclofenac, naproxen, etoricoxib)
    - Disease modifying anti-rheumatic drugs (DMARDs – hydroxychloroquine, methotrexate, azathioprine, mycophenolate)
    - steroids (oral, intra-articular)
  - Neurological
    - epilepsy (anti-epileptic), depression (anti-depressants), psychosis (anti-psychotics) ± steroids and cyclophosphamide
  - Serositis – steroids ± cyclophosphamide
  - Renal – steroids and cyclophosphamide or mycophenolate ± dialysis and transplantation
  - Antiphospholipid antibody syndrome – aspirin, heparin, warfarin
  - Severe and major organ involvement – Steroids first, then Biologics therapy – Rituximab (B-cell depleter), Belimumab (monoclonal anti-Blys)

- Hydroxychloroquine useful for preventing flares and helpful for fatigue, has anti-clotting effects and improves lipid profile

LS Teh 2010
Scleroderma

- Characterised by fibrosis and vascular problems
  - Female to male ratio 4:1
  - 1 in 1000
  - Less common in Asians

- Types
  - Localised
    - Morphoea
  - Systemic
    - Limited cutaneous (lcSS), CREST
    - Diffuse cutaneous (dcSS)

- Autoantibodies
  - ANF 90%
  - Topoisomerase - Scl-70 30%
  - Centromere 90%

- Presents with Raynaud’s phenomenon

- Skin - shiny and thickened
  - hands, face (lsSS)
  - Proximal arms, legs and trunk (dcSS)
  - Calcinosis and telangiectasis
  - Digital ulcers

- Lung – fibrosis and pulmonary hypertension
- Kidney - hypertension
- Joints – arthralgia, myalgia
- Gastrointestinal
  - Heartburn and oesophagitis
  - Intestinal dysmotility – constipation and diarrhoea

LS Teh 2010
Visible features of scleroderma

Dilated, irregular capillaries with avascular areas in nailfold
CREST syndrome and Art

Paul Klee (1879-1940) – Swiss German painter influence by cubism, expressionism, surrealism and orientalism. Friend of Kandinsky – Russian painter
Management of Scleroderma

- No treatment for the skin condition
  - In dcSS, aggressive disease for 7-10 years and then stabilises and can sometimes soften
- Depends on organ involved
  - Raynaud’s – keep warm, heated gloves, calcium channel antagonists (nifedipine), iloprost infusions
  - Lung
    - fibrosis – steroids ± cyclophosphamide
    - Pulmonary hypertension – endothelin-1 receptor antagonist (bosentan), vasodilator – iloprost, sildenafil (viagra)
  - Renal – Angiotensin converting enzyme inhibitor (ACEI – lisinopril, ramipril)
  - GI tract – proton pump inhibitor for oesophagitis, motility drugs, antibacterials for overgrowth syndrome, surgical

LS Teh 2010
Myositis

- Usually there is inflammation of muscle
  - Slightly more common in women ratio 2:1
  - 0.5 to 8.4 per million
  - More common in Afro-Caribbeans and less common in Japanese

- Type
  - Dermatomyositis (with rash) DM
  - Polymyositis (without rash) and may have underlying malignancy PM
  - Focal myositis
  - Amyopathic dermatomyositis (typical rash but no evidence of muscle involvement)
  - Drug induced
  - Inclusion body myositis (more common in men)

- Autoantibodies
  - Antinuclear antibodies 90% DM, 50% in PM
  - Rheumatoid factor 50% in PM
  - Anti-synthetase (Jo-1, Mi-2) 30%

- Muscle
  - Weakness in limb muscles
  - Sometimes tenderness in muscles
  - Difficulty swallowing
  - Heart muscle rarely affected

- Skin
  - Raynaud’s
  - Purplish rash over eyelids
  - Purple spots on bony prominences
  - Photosensitive rash
  - Nailfold capillary dilatation
  - Telangiectasia
  - Calcinosis in children
  - Cracked skin – “mechanic’s hands”

- Lungs (esp with Jo-1 ab)
  - Inflammation and fibrosis

- Gastrointestinal
  - Dysphagia, oesophagitis, constipation

- Arthritis/arthralgia

- Renal disease rare

- Non-organ specific symptoms
  - Morning stiffness, fatigue, anorexia, fevers and weight loss

LS Teh 2010
Visible signs of Dermatomyositis

Heliotrope rash over eyelids

Grotton’s papules

LS Teh 2010
Management of Myositis

- Muscle disease
  - high dose steroids and steroid sparing agents such as azathioprine, methotrexate
  - Cyclophosphamide
  - Intravenous immunoglobulins
  - Physiotherapy

- Skin disease
  - Symptomatic treatment of Raynaud’s

- Lung disease
  - Steroids ± cyclophosphamide
**Sjogren’s syndrome**

- Also known as Mikulicz disease or Sicca syndrome
  - Inflammation and damage to exocrine
  - Female to male ratio 9:1

- **Types**
  - Primary
  - Secondary
    - SLE
    - Rheumatoid arthritis

- **Autoantibodies**
  - Antinuclear antibodies 90%
  - Ro/SSA 75% (15%) or La/SSB 40-50%
  - Rheumatoid factor 90%

- **Exocrine gland dysfunction**
  - Dry eyes
  - Dry mouth with salivary gland enlargement
  - Dry skin
  - Dry nose
  - Vaginal dryness

- **Vasculitis**
  - Skin rash and ulceration
  - Neuropathy

- **Renal – interstitial nephritis**

- **Arthalgia/Arthritis**

- **Gastrointestinal**
  - Oesophagitis

- **Non-specific symptoms – fatigue, weight loss, anorexia**
Sjogren’s syndrome

- **xerophthalmia**
- **Schirmer’s test**
- **Parotid gland +++**
- **xerostomia**

LS Teh 2010
Vasculitis

LS Teh 2010
Management of Sjogren’s syndrome

- **Eyes**
  - Artificial tears
  - Humifier
  - Surgical – punctal plugs to retain tears

- **Mouth**
  - Artificial saliva
  - Oral hygiene
  - Salivary stimulation – Pilocarpine

- **Skin** – moisturising agents

- **Nose** – nasal sprays

- **Lungs** – humifiers

- **Vaginal dryness** - moisturizers

- **Arthralgia/Arthritis** – NSAIDs, DMARDs (hydroxychloroquine, methotrexate)

- **Vasculitis** – steroids and immunosuppressive drugs, local treatment and surgical
Raynaud’s

- **What is Raynaud’s phenomenon?**
  In 1862, a French physician, Auguste-Maurice Raynaud in his thesis “Local asphyxia and symmetrical gangrene of the extremities” described for the first time color changes of the hands and feet triggered by exposure to cold temperatures.
  - Today we call this exaggerated response to cold “Raynaud’s phenomenon” in his memory
  - Tricolour changes – white to blue to red on recovery
Raynaud’s

- **As defined**
  - Female to male ratio 5:1
  - Primary form twice as common as secondary
  - Common disease in young women

- **Types**
  - Primary (Rayaud’s disease)
  - Secondary
    - CTD (Scleroderma, SLE, RA, myositis)
    - Drug induced
    - Arterial disease
    - Neurological disorders
    - Occupation
    - Miscellaneous

- **Autoantibodies**
  - None in Primary

- **Triggers of Raynaud’s**
  - Cold
  - Temperature change
  - Emotional
  - Psychological upsets

- **Colour changes**
  - White then blue and then red on rewarming

- **Numbness**

- **Pain**

- **Sites**
  - Usually hands
  - Can affect feet
  - Nose
  - Earlobes

LS Teh 2010
Raynaud’s

Thermography of hands

LS Teh 2010
Management of Raynaud’s

- **Simple measures**
  - Keep warm including body, gloves (heated), avoid changes in temperature, ensure house insulated well
  - Stop offending drug or exposure to triggering process
  - Stop smoking
  - Counselling or relaxation therapy
  - Swinging arms to improve circulation

- **Medication**
  - Calcium channel blockers (nifedipine, diltiazem)
  - Vasodilators (sildenafil)
  - Intravenous prostacyclin
  - Sympathectomy
  - Treat underlying CTD
Acknowledgements

- DermNet NZ – http://dermnetnz.org
- http://www.medicinenet.com
- Google images – www.google.com