1. Systemic autoimmune disease

1. Introduction

The systemic or non organ-specific autoimmune diseases were initially described, characterised and categorised using the features present in the history obtained from patients who suffered from them, and the findings on clinical examination. The disease definitions take into account also the clinical course of the conditions, and the findings on detailed laboratory investigation using various kinds of laboratory tests. Although the diseases have been categorised into certain types, the situation is made complicated by the fact that (as with most human disease of whatever cause) there is great variation amongst patients because:

Different combinations of the many clinical manifestations of any given condition may be present in different patients
The severity of any given clinical manifestation varies greatly between patients
The severity of any given clinical manifestation can change in the same patient over time
Overlap syndromes may exist between separate conditions, or evolve in a given patient

2. Rheumatoid arthritis

Rheumatoid Arthritis (RA) is characterised by persistent inflammation of the synovium leading to varying degrees of joint destruction. The disease is associated with HLA-DR4 and HLA-DR1 and occurs more frequently in women. The target autoantigen is unknown, although type II collagen is a candidate. It is possible that in situations of heavy tissue catabolism (as occurs in RA joints) peptides might be generated from self-antigens that stimulate the clonal expansion of T cells which have escaped negative selection in the thymus (i.e. activate T cells in a state of clonal indifference, see section 3).

The disease characteristically starts in the small joints (although spares the distal interphalangeal joints), and then spreads to involve more proximal joints. The synovial membrane undergoes infiltration by lymphocytes (lymphoid follicles arise) causing villous hypertrophy. MHC class II molecules are strongly expressed on B cells and synovial lining cells. It is thought that the autoantigen is presented to T cells at this site and that autoantibody production (against immunoglobulins, histones, DNA, collagen) results in immune complex formation. These are phagocytosed by macrophages and neutrophils, leading to their activation, formation of reactive oxygen intermediates and release of lysosomal enzymes and thus tissue damage. Release of IL1 and TNF may activate chondrocytes and osteoclasts causing further tissue damage.

A high proportion of patients with RA have autoantibodies called rheumatoid factor in their serum. These are autoantibodies directed against the Fc region of human IgG, and may be of the IgM, IgG or IgA class, although IgM rheumatoid factors are the ones most frequently present in RA. There are also many extra-articular (i.e. non-joint) manifestations of RA. The American Rheumatism Association criteria are widely used in the diagnosis of RA.

3. Systemic lupus erythematosus

Systemic Lupus Erythematosus (SLE) is the classical systemic autoimmune disorder. The prevalence is around 1/700 and the annual incidence of new cases is about 5/100 000. The peak incidence for females is in late middle age, and is somewhat later for males. In all age groups except neonates, lupus is more common in females than males. The F:M sex ratio in children is about 2:1, increasing to 6:1 after puberty and peaking at 9:1 in late adulthood. In the over 60 age group the sex ratio declines to 3:4:1. Case control studies have failed to demonstrate any affect of age at menarche, age at first pregnancy, or parity on the disease incidence.

Aetiological data obtained from epidemiological studies have revealed familial clustering. The incidence of SLE in first degree female relatives of affected patients has been estimated at 2-15%. Concordance in monozygotic twins is 25-60%, compared with around 10% in dizygotic twins.

Mortality data indicates that neither age at diagnosis nor sex influence survival. The most important predictors of survival are renal and CNS involvement. Both elevated serum creatinine and persistent proteinuria predict premature death from lupus. Specific immunological parameters (e.g. autoantibodies, hypocomplementaemia) are not predictive of survival. The most common causes of death in patients with SLE are active renal and CNS disease, infection, and premature coronary artery disease (related to glucocorticoid therapy).

Although this is a multisystemic disorder, most patients present with isolated manifestations which may lead to confusion with disorders such as ITP, primary Raynauds, or rheumatoid arthritis. Skin and joint manifestations are the presenting feature in about 75%. Most patients have constitutional symptoms. Other clinical features include glomerulonephritis, lymphadenopathy, anaemia and leucopenia, pleurisy, mouth ulcers, and CNS disease. To assist in the diagnosis of SLE the American Rheumatism Association has defined a list of 11 criteria and if a patient has 4 more of these over a period of time, may have Lupus.
4. **Scleroderma**

**Classification**

I. **Limited (CREST syndrome)**
- Long-standing Raynauds
- Skin changes limited to hands, face, feet and forearms
- Skin calcification and telangiectasia
- GIT involvement
- Late pulmonary hypertension
- Dilated nailfold capillary loops without drop-out.

II. **Diffuse (Systemic sclerosis)**
- Truncal and acral involvement
- Skin changes within one year of Raynauds onset
- Tendon friction rubs
- Early interstitial lung disease
- Diffuse GIT involvement
- Nailfold capillary dilation and drop-out.

**Pathogenesis**

Scleroderma is a state of dysregulated connective tissue deposition. It is characterised by expansion of dysregulated fibroblast clones which behave autonomously and overexpress genes encoding elements of the extracellular matrix, particularly type I collagen. There is also evidence of an underlying autoimmunity: MHC associations, autoimmune serology, familial association with other autoimmune diseases, predominant inflammatory perivascular infiltrate with activated T cells in regions of fibrosis, and the resemblance to graft versus host disease. Fibroblasts can be activated by a number of T cell derived cytokines and this may provide one link between immune activation and the pathology of scleroderma.

Systemic sclerosis is a profoundly debilitating condition, due to the effects on the skin and gastrointestinal tract. As well as causing significant morbidity, it also has a high mortality (~40% over 5 years), due to pulmonary fibrosis, and renal involvement. CREST syndrome (Calcinosis, Raynaud's phenomenon, Esophageal dysmotility, Sclerodactyly and Telangiectasia) is characterised by limited cutaneous involvement, although severe Raynauds and calcinosis can still lead to severe functional limitations. Renal involvement does not usually occur in the limited form, but respiratory involvement in the form of pulmonary hypertension may be a significant problem. 60-70% of patients with CREST have anti-centromere antibodies.

5. **Sjögren's Syndrome**

Sjogrens syndrome (SS) is a relatively common autoimmune disorder characterised by exocrinopathy resulting in the cardinal manifestations of keratoconjunctivitis sicca (90%) and xerostomia (80%). When these manifestations occur in the absence of another clearly defined connective tissue disease, the diagnosis is primary Sjogren's syndrome. Secondary SS may occur in association with a variety of other autoimmune diseases. However, primary SS is best not thought of as simply a diagnosis of exclusion as there appears to be a discrete pattern of extraglandular involvement which may accompany the sicca complex.

Women are disproportionately affected (90%), and the mean age of presentation is around 52 years. HLA B8, DR3, DR2 and DRw52 are over-represented in patients with SS.

**Glandular Manifestations**

1. Keratoconjunctivitis sicca - Diminished tear production is due to destruction of the active secretory apparatus. The tears are quantitatively and qualitatively altered, with increased osmolarity, diminished IgA, lysozyme and lactoferrin content. Patients may report dry eyes, grittiness, burning, photophobia, or reduced visual acuity.

2. Xerostomia - Diminished saliva production may manifest as a dry mouth, odynophagia, halitosis, excessive oral pathology and infections, and dysgeusia.

**Extraglandular manifestations of Sjögrens Syndrome.**

1. Respiratory disease - Dryness of the upper and lower respiratory tract may lead to inspissated secretions, chronic cough and recurrent infection. Interstitial infiltrates also occur. In addition, serositis with pleural effusions may predominate.
2. Renal Disease - Interstitial nephritis and tubular dysfunction, most commonly manifesting as renal tubular acidosis, but may progress to complete Fanconi's syndrome.

3. Neurological - Peripheral and cranial neuropathy have been associated with SS. In addition, CNS involvement has been described in a small minority of patients in which multifocal lesions occur throughout the white matter resembling MS both clinically and radiologically.

4. Arthritis

5. Raynaud's phenomenon

6. Cutaneous vasculitis

7. Non-Hodgkin's lymphoma - occurs with increased frequency, often in the mucosa-associated lymphoid tissue.

6. The antiphospholipid syndrome

Antiphospholipid antibodies occur in patients with lupus, but also in patients who do not fulfill the diagnostic criteria for lupus. In both cases they are associated with several well-defined clinical manifestations:

1. Thromboses – in about 40%. Distinguished from other prothrombotic disorders by the presence of both arterial and venous thromboses (other thrombotic syndromes usually involve either arterial or venous circulations). Emboli from thrombi on heart valves may also occur.

2. Foetal loss - about 40%. APLAS accounts for about 4% of cases of recurrent foetal deaths

3. Thrombocytopenia - 30-40%

4. Coomb's test positive haemolytic anaemia

Other associations which are less clearly established include chorea, cardiac valvular disease and myocardial infarction.


The co-ordinated and stereotypical early response to tissue damage or infection mediated by the innate immune system is described as the acute phase response (APR). The APR is initiated by cytokines and other secretory products of macrophages and/or blood monocytes, which are activated during acute inflammation. The acute phase response is an altered pattern of protein synthesis by the liver, which represents a vestigial innate immune response. The are a large number of proteins that are secreted during an APR, but the most dramatic response occurs with C-reactive protein (CRP). Thus, measuring CRP is often used as an indicator of tissue damage or inflammation. Another common indicator of the APR is the erythrocyte sedimentation rate (ESR), which is influenced by a number of different acute phase reactants.

An unusual feature of SLE is that despite causing generalised inflammation and often tissue damage, the autoimmune process fails to stimulate a normal APR and CRP is not increased. However, intercurrent infections can stimulate a relatively normal CRP response, which provides a useful way of distinguishing disease activity from infection. In contrast to SLE, the inflammation of RA stimulates a significant CRP response. Other non-specific markers of inflammation include polyclonal hypergammaglobulinaemia (especially in Sjogren's syndrome) and thrombocytosis.

Complement components C3 and C4 are also acute phase reactants. However, they may be low in states of complement consumption, as occurs with active SLE. Interpretation of complement studies in patients with SLE is even more complicated because inherited complement deficiencies predispose to SLE. For example, a low C4 may reflect consumption, or a deficiency of one or more of the four C4 alleles.

8. Autoantibodies in systemic autoimmunity

1. Overview of Nuclear Antigens

a. The Structure of the Human Cell Nucleus- The nuclear membrane is a bilaminar structure with pores to allow molecules to move between the cytoplasm and the nucleus. The outer nuclear membrane is continuous with the endoplasmic reticulum (ER). The inner membrane contains lamina molecules, which provide sites of attachment for chromatin. Of the nuclear contents, the major autoantibody targets are chromatin, nucleoli and ribonucleoproteins (RNPs).
b. Chromatin - Chromatin consists of DNA and histone proteins. 146 base pairs (bp) of DNA are wound in almost two turns around 8 histone molecules to form nucleosomes. Nucleosomes are connected by strands of 60 bp (linker DNA) which associate with H1 histones. Chromatin is usually insoluble in physiological buffers (c.f. RNP which is soluble; both are labile).

c. Nucleoli - The nucleoli are the largest and most complex RNP structures. They are the sites of assembly of subunits of ribosomes. Nucleoli disappear at the time of cell division, then reform at the nucleolar organizing regions (NORs) which occur at the tips of the short arms of chromosomes 13, 14, 15, 21 and 22. The genes for ribosomal RNA are found at these sites. The enzyme RNA Polymerase I occurs only in the nucleolus and is responsible for the transcription of ribosomal RNA.

d. Ribonuclear proteins - The so-called extractable nuclear antigens (ENAs) are mostly small nuclear and small cytoplasmic RNP's involved in processing RNA. nRNP and Sm antigens are U series RNP's, which are components of the spliceosome and are involved in the removal of the introns from heterogenous nuclear RNA. The SS-B antigen is a 48 kD protein which acts as a termination factor for RNA Polymerase III.

2. Antinuclear Antibodies

Patients with SLE usually have multiple autoantibodies, but those which are most specific for SLE are directed at dsDNA and Sm. Antibodies to histones also occur in SLE. Antibodies to all classes of histones have been demonstrated in SLE and have also been demonstrated in other disorders. Antibodies to histones are responsible for the LE cell phenomenon, now only of historical interest. Antibodies to histones are common in drug-induced lupus. See some images of staining patterns here.

Clinical Relevance of ANA

There are certain limitations in using ANA as a screening test.

i. 20% of healthy relatives of patients with systemic autoimmune disease may have positive ANAs.
ii. 75% of elderly patients who are healthy and 2% of healthy non-elderly individuals may have a positive ANA.
iii. ANA alone is a weak test for: Sjogren's syndrome, scleroderma and polymyositis

Anti-dsDNA Antibodies

About 65% of SLE patients with active disease have anti-dsDNA antibodies but less than 5% have elevated levels when disease is quiescent. More than 80% of patients with lupus nephritis have elevated levels. Anti-dsDNA antibodies are directed towards the sugar-phosphate backbone of the DNA molecule, and when present in high concentration (e.g. > 50 IU/ml) make a diagnosis of SLE very likely. Antibodies to single-stranded DNA are directed towards the nucleotide bases in DNA and are found in many conditions including SLE, RA, other inflammatory diseases, chronic infections and malignancies. Anti-dsDNA antibodies play a role in the pathogenesis of SLE but a similar role for the other autoantibodies in SLE or other diseases has not yet been well established.

3. Anti-Histone Antibodies

Associated with SLE, drug-induced SLE and in a minority of other connective tissue disorders.

Antigens recognised in Drug-induced lupus
H2A, H2B Drug-induced lupus, Procainamide, Hydralazine, methyldopa, penicillamine, quinidine, INH.
H2A, H2B-DNA complex Quinidine, Procainamide (more specific but not for hydralazine, however, idiopathic lupus serum will also be positive).

*IgM anti-histone antibodies occur in patients on drugs associated with lupus but who are asymptomatic. IgG antibodies occur in those who are symptomatic.

Extractable Nuclear Antigens (ENAs)

ENAs are a diverse cluster of antigens grouped together because they can be extracted from nuclei and solubilised in saline. They include SS-A, SS-B, RNP, Sm, Jo-1, and Scl-70. The presence of antibodies to ENAs is suggested by speckled immunofluorescence on the ANA. These proteins are intimately associated with various RNA molecules and are thus called ribonucleoproteins, but the nomenclature used for them is often a source of confusion. Sm, Ro and La were named after the first two letters of the surnames of the patients in whom they were first found. Two proteins associated with Sjogren's Syndrome were independently described as antigens A and B, but are now known to be identical to Ro and La respectively (i.e. SS-A = Ro and SS-B = La)
### Antibodies to RNA-Associated Proteins

There are two pairs of closely associated autoantibodies which occur in systemic autoimmunity:

#### i. Sm and nRNP Antibodies

RNP and Sm are small nuclear ribonucleoproteins (snurps) that form part of the spliceosome, involved in the removal of introns from mRNA. Sm is specific for SLE (but only occurs in 20-30% of patients) and when present is predictive of renal disease (RNP alone predicts against renal disease).

#### ii. SS-A and SS-B Antibodies

SS-A (also called Ro) and SS-B (also called La) are found in both nucleus and cytoplasm. Their precise location varies with the stage of the cell cycle. SS-A antibodies react with at least four proteins of mw 60, 60, 54 and 52 kDa complexed with 4-5 small RNA particles called hY RNAs (hY stands for human cytoplasm; hY1, hY3, hY4, hY5). As with the antigens for Sm and nRNP, the antigens reside on the protein moieties, not on the RNA although the RNA may be necessary to maintain the conformation of the epitope. SS-B reacts with a 48 kDa protein complexed with nascent RNA polymerase III transcripts. This protein (48kD) is a transcription termination factor for RNA polymerase III and is primarily located in the nucleus. This protein may have a role in the nucleocytoplastic transport of RNA. There is some evidence that this protein can associate with hY5 RNA leading to the association between SS-A and SS-B.

Clinical associations of SS-A include subacute cutaneous lupus, C2 and C4 deficiency, photosensitivity, neonatal lupus, rheumatoid factor-positive lupus, renal involvement in patients with SLE and pneumonitis.

SS-B is highly specific for Sjogren’s syndrome.

#### Summary of some relatively specific autoantibodies

<table>
<thead>
<tr>
<th>AutoAb</th>
<th>Specific for</th>
<th>AutoAb</th>
<th>Seen most often in</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sm</td>
<td>SLE</td>
<td>(U1) RNP</td>
<td>SLE, MCTD</td>
</tr>
<tr>
<td>Jo-1</td>
<td>Dermato-/poly-myositis</td>
<td>SSA/Ro</td>
<td>Sjogren's (60%), SLE (35%)</td>
</tr>
<tr>
<td>Centromere</td>
<td>CREST syndrome</td>
<td>SSB/La</td>
<td>Sjogren's (40%), SLE (15%)</td>
</tr>
</tbody>
</table>

### Autoantibodies of Inflammatory Muscle Disease

Inflammatory autoimmune muscle diseases include polymyositis (PM), dermatomyositis (DM) and inclusion body myositis (IBM). 90% of patients with myositis have at least one autoantibody. Most of these recognise cytoplasmic antigens so they are often ANA negative.

#### i. Antibodies to Cytoplasmic Antigens, aminoacyl-tRNA synthases

<table>
<thead>
<tr>
<th>AutoAb</th>
<th>Specific for</th>
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<th>Seen most often in</th>
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<tr>
<td>Sm</td>
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<td>(U1) RNP</td>
<td>SLE, MCTD</td>
</tr>
</tbody>
</table>
6. Autoantibodies in Scleroderma

About 95% of scleroderma patients have circulating autoantibodies and around 90% have positive ANAs.

i. Anti Centromere Antibodies

Anti centromere are directed to metaphase chromatin, specifically, the kinetochore and are associated with CREST syndrome (present in about 90% of cases), primary Raynaud's (10-20%), primary biliary cirrhosis.

ii. Scl-70 Antibodies

Antibodies to Scl-70 react with DNA topoisomerase I, which is involved in the relaxation of supercoiled DNA during transcription. The antibodies to Scl-70 in scleroderma are able to inhibit the supercoiling of DNA. Scl-70 antibodies are almost exclusive to scleroderma, but also in a small minority of patients with primary Raynauds disease and are predictive of more extensive disease. Scl-70 antibodies are detected in about 25% of patients with scleroderma, and are more common in Negroes than Caucasians. Scl-70 antibodies correlate with a more severe clinical course with more extensive visceral disease and proximal skin tightening. In females, Scl-70 confers an increased risk of malignancy.

7. Antiphospholipid antibodies

Two types of phospholipid antibody may be detected

i. Cardiolipin antibodies

Autoantibodies directed against a complex of a cardiolipin, a phospholipid, and β 2-glycoprotein 1 (a serum glycoprotein which binds to phospholipids).

ii. Lupus Anticoagulant

The lupus anticoagulant (LA) is directed against the phospholipid portion of the prothrombin activator complex. The LA has been defined as an antibody that interferes with phospholipid-dependent coagulation tests without inhibiting the activity of specific clotting factors. The antigen here is probably thromboplastin, which contains several phospholipids but not cardiolipin.

The criteria for the recognition of a LA are:
1. Abnormality of a phospholipid-dependent clotting test, e.g. APTT.
2. The abnormality must be due to an inhibitor of clotting, not a clotting factor inhibitor etc. Thus, mixing studies must be performed.
3. The inhibitor must be directed at PL. Thus, the abnormality should be corrected by the addition of phospholipid or activated platelets.

It should be remembered that 70% of patients who have these antibodies are asymptomatic.

9. Vasculitis

Vasculitis is inflammation of blood vessel walls, which can result in impairment of function of the tissues supplied with blood by the blood vessels concerned, and even infarction of the tissues subtended. For reasons that are still not entirely clear, different vasculitides have a predilection for different combinations of organs - it is possible that this may be due to the restricted or differential expression in the endothelia of these organs of molecules essential for the immunopathological process to occur. There are many causes and types of vasculitis. One way to consider them is in terms of the size of the vessel affected.

Classification

I. Large Vessel Vasculitis

Takayasu arteritis
Giant Cell arteritis

II. Medium sized Vessel Arteritis
Classic polyarteritis nodosa
Kawasaki disease

**III. Small Vessel Vasculitis**

ANCA-associated Wegener's granulomatosis
Microscopic polyarteritis
Churg-Strauss syndrome
Primary pauci-immune necrotising and crescentic glomerulonephritis
Drug-induced (hydralazine, propylthiouracil)
Anti-GBM disease
Mixed cryoglobulinaemia (hepatitis C)
Henoch-Schonlein purpura
Primary cutaneous leucocytoclastic vasculitis
Thromboangiitis obliterans
SLE
Rheumatoid arthritis

10. **ANCA-Associated Vasculitis**

The approach to vasculitis has been radically changed by the identification of anti-neutrophil cytoplasmic antibodies (ANCA) which are helpful in the diagnosis of vasculitis. Most importantly, ANCA occurs with Wegener’s granulomatosis, Churg-Strauss vasculitis and microscopic polyarteritis nodosa (mPAN). ANCA may play an important part in initiating disease, although cellular immune mechanisms probably play a critical and determining role subsequently. There are two principal patterns of ANCA, termed cytoplasmic ANCA, where the target antigen is Proteinase 3, and perinuclear ANCA, where the antigen is Myeloperoxidase. Most patient's (90%) with Wegener’s granulomatosis have a positive cANCA and about 50% of patients with mPAN are also positive. However, cANCA and pANCA can be seen in a variety of other disorders including infections, chronic liver and inflammatory bowel disease. CRP and ANCA levels can be used to monitor disease activity.

11. **Glomerulonephritis**

The term glomerulonephritis is applied to immunologically-triggered inflammation which is largely confined to the glomerular tuft. The high glomerular filtration pressure and the process of ultrafiltration increase the kidneys' susceptibility to potentially toxic substances in the circulation. There are several basic mechanisms of GN

1. Circulating immune complexes (of whatever origin/cause) tend to be deposited at the glomerulus. Complement activation frequently follows, with ensuing infiltration by cells, and further inflammation. There are many causes of glomerulonephritis, which has been classified histologically. However, there is no simple relationship between the histological appearances and the clinical features. A large variety of infections are associated with glomerulonephritis because immune complexes are deposited in the kidney. The pattern of damage is at least partly determined by the isotype of the immunoglobulin deposited, IgA complexes being less damaging than IgG. Some of the clinical syndromes and useful investigations are outline below.

2. Autoantibodies targeted to glomerular antigens – Goodpasture's disease is due to the presence of anti-glomerular basement membrane antibodies directed against type IV collagen which bind to glomerular and pulmonary basement membranes causing glomerulonephritis and haemoptysis. It is rare but rapidly progressive, the prognosis being directly related to the degree of renal failure at presentation. Without treatment 75-90% of patients die. It may be diagnosed by looking for anti-GBM autoantibodies in serum and on renal biopsy.

3. Systemic vasculitis- frequently involves the glomerular tuft, e.g. Wegener's granulomatosis, mPAN.

12. **Clinical Manifestations of Glomerulonephritis**

The glomeruli have a limited number of ways of responding to immunological insults, which give rise to a number of clinical syndromes.

1. Acute nephritis- haematuria, proteinuria, hypertension and oliguria (Exclude obstruction)
2. Nephrotic syndrome- hypoalbuminaemia, oedema and proteinuria (>3.5g/day)
3. Proteinuria- >300mg/day but without nephrotic syndrome
4. Haematuria- (exclude lesion in upper/lower urinary tract)
5. Renal Failure- acute or chronic Often caused by glomerulonephritis
**Cryoglobulinaemia**

Cryoglobulinaemia is the presence in serum of immunoglobulins which precipitate on cooling, and this may occur as a primary disorder or secondary to another disease. The clinical features are caused by the obstruction of small blood vessels and the ischaemia and possible infarction of the tissues which they subtend. They are classified into 3 types:

**Type I (25%)** are monoclonal (usually IgM) associated with lymphoproliferative disease

**Type II (25%)** are mixed (monoclonal + polyclonal) with rheumatoid factor activity and associated with lymphoproliferation and hepatitis C

**Type III (50%)** are polyclonal and associated with various non-organ-specific autoimmune diseases and hepatitis C.

<table>
<thead>
<tr>
<th>Clinical syndrome</th>
<th>Pathogenesis</th>
<th>Useful investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Membranous Nephropathy (proteinuria, haematuria or nephrotic syndrome)</td>
<td>Chronic deposition of immune complexes. Association with HLA DR3, can occur with some drugs, chronic infections</td>
<td>Renal biopsy shows thickening GBM with granular deposits of IgG and C3(also IgA and IgM) C3 normal</td>
</tr>
<tr>
<td>Membrano proliferative GN (MPGN) (acute nephritis, nephrotic syndrome) type II associated with partial lipodystrophy</td>
<td>2 types: type II is associated with antibodies to the C3 convertase, stabilising the complex and leading to C3 consumption with normal C4</td>
<td>Renal biopsy in type I disease shows lgs and C3. In type II, C3 alone is deposited. C3 is low in type II. Can be low or normal in type I disease</td>
</tr>
<tr>
<td>All patterns in SLE</td>
<td>Diffuse proliferative GN, membranous GN, MPGN</td>
<td>ANA, ds DNA, C3, C4. Renal biopsy shows variable pattern with deposition of IgG and C3</td>
</tr>
<tr>
<td>Goodpasture's syndrome (acute nephritis, acute renal failure, haematuria, pulmonary haemorrhage)</td>
<td>Typically male smoker's. Can be post infectious. Abs against glomerular basement membrane DR2 associated</td>
<td>Anti-GBM abs in serum. Linear staining of IgG on GBM</td>
</tr>
<tr>
<td>ANCA associated GN (acute nephritis, renal failure, haematuria)</td>
<td>cANCA (Proteinsase 3) particularly associated with Wegener's Granulomatosis pANCA (Myeloperoxidase) often associated with microscopic Polyarteritis. Renal biopsy shows necrosis often with crescentic GN. Not much in the way of lgs and Complement</td>
<td></td>
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<tr>
<td>IgA Nephropathy (haematuria, typically after respiratory infection, can present as acute nephritis or nephrotic syndrome)</td>
<td>IgA immune complexes deposited in the Mesangium HLA-DR4 associated</td>
<td>Renal biopsy shows IgA, C3</td>
</tr>
<tr>
<td>Henoch Schonlein Purpura. Purpuric rash typically over extensor surfaces associated with infection</td>
<td>IgA immune complexes give rise to skin and renal lesions</td>
<td>Renal Biopsy shows IgA and C3 as in IgA nephropathy</td>
</tr>
<tr>
<td>Minimal change nephritis (nephrotic syndrome)</td>
<td>Pathogenesis unknown. Responds to steroids often. Proteinuria is selective (albumin)</td>
<td>Renal biopsy no lgs or complement</td>
</tr>
<tr>
<td>Amyloidosis (nephrotic syndrome, renal failure</td>
<td>associated with light chain disease in myeloma, Also primary amyloidosis</td>
<td>Characteristic birefringent staining with congo red</td>
</tr>
</tbody>
</table>

**Diseases associated with Glomerulonephritis**

<table>
<thead>
<tr>
<th>Type</th>
<th>Antigen</th>
<th>Disease</th>
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<tbody>
<tr>
<td>Virus</td>
<td>Hepatitis B</td>
<td>Polyarteritis nodosa</td>
</tr>
<tr>
<td></td>
<td>Hepatitis C</td>
<td>Mixed essential cryoglobulinaemia</td>
</tr>
<tr>
<td></td>
<td>Cytomegalovirus</td>
<td>Glomerulonephritis</td>
</tr>
<tr>
<td>Bacteria</td>
<td>Streptococcal</td>
<td>Acute PS GN</td>
</tr>
<tr>
<td></td>
<td>Streptococcal viridans</td>
<td>Endocarditis</td>
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<tr>
<td></td>
<td>Staphylococci Albus</td>
<td>Shunt Nephritis</td>
</tr>
<tr>
<td></td>
<td>Mycobacterium leprae</td>
<td>Lepromatous leprosy</td>
</tr>
<tr>
<td>Parasites</td>
<td>Plasmodium Malariae</td>
<td>Malaria</td>
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<tr>
<td>Schistosoma</td>
<td>GN</td>
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<tr>
<td>Toxoplasmosis</td>
<td>GN</td>
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<tr>
<td>Drugs</td>
<td>Penicillamine</td>
<td>Drug nephritis</td>
</tr>
<tr>
<td>Gold</td>
<td>Drug nephritis</td>
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<tr>
<td>Foreign proteins</td>
<td></td>
<td>Serum sickness</td>
</tr>
<tr>
<td>Autoantigens</td>
<td>DNA, nuclear Ag</td>
<td>SLE</td>
</tr>
<tr>
<td>IgG</td>
<td>Cryoglobulinaemia</td>
<td></td>
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<tr>
<td>Tumour Ag</td>
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<td>Neoplasia</td>
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