# DISEASES OF THE IMMUNE SYSTEM

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# Note on References

**See box to the right for reference notations.**

**PubMed references usually link to abstracts, which provide useful information. But most abstracts link to a free, full-text article for in-depth reading.**

**Image references usually link to a whole page of images. The images themselves may be useful, but care must be taken to ensure that they relate to the topic of the text. Images are most valuable as a gateway to publications related to the topic. Clicking on the image will take you to the publication. However, to get the full publication it sometimes may be necessary to copy the url and transfer it to your browser.**

- **Reference notations: when references are listed, the following suffixes indicate:**
- **pm = PubMed**
- **w = Wikipedia**
- **i = Images (usually Google images)**
- **rg = ResearchGate**
- **yt = YouTube**
- **sd = Science direct**
- **ow = Other website**
- **Selected text = PubMed, Wikipedia, or images**

# What are the types of disease of the immune system?

- Primary immunodeficiencies (usually genetic)
- Acquired immunodeficiencies (e.g. HIV; iatrogenic causes such as therapeutic bone-marrow suppression; cancer, malnutrition, renal disease)
- Autoimmune disorders

# What are major examples of primary immune deficiencies?

- Isolated IgA deficiency
- Common variable immunodeficiency
- X-linked agammaglobulinemia
- DiGeorge Syndrome
- Severe combined immunodeficiency

# What is the most common immune deficiency?

- Isolated IgA deficiency (1w, 2i) has a prevalence of 1:700.
- Deficiency of IgA signifies that mucosal defenses against pathogens are weakened.

Often asymptomatic, but patients with this condition may be prone to sino-pulmonary infections and diarrhea.

# What is common variable immunodeficiency?

- Common variable immunodeficiency (CVID) (1pm, 2i, 3ow, 4pm) is a condition characterized by recurrent infections and low antibody levels. The most common deficiencies are immunoglobulin (Ig) types IgG, IgM and IgA.

- CVID is a lifelong disease that predisposes to chronic lung disease and inflammation and infection of the gastrointestinal tract. It is characterized by an abnormally low level of immunoglobulins in the blood.

# What are the major features of common variable immunodeficiency?

## Features of common variable immunodeficiency

- Mature B-cells are present, but plasma cells are not.
- The cause of failed B-cell differentiation may be defects of the B-cells, failure of T-cells to stimulate differentiation, or inappropriate suppression by T-cells.
- Onset is usually between ten and thirty years of age.
- Characteristically a diagnosis of exclusion where repeated and chronic infections are common and other forms of immunodeficiency are ruled out.

# What is X-linked agammaglobulinemia?

- X-linked agammaglobulinemia (1pm, 2i) is also known as Bruton disease.
- Pre-B-cells are unable to differentiate into mature B-cells.
- B-cells are sparse or absent in the bloodstream; levels of immunoglobulins are low.
- Typically suspected when a young boy (X-linked recessive disease) has repeated, chronic bacterial (and some types of viral) infections. Normally appears first at the age of 6 months, as the levels of maternal immunoglobulins drop.

# What is DiGeorge Syndrome?

- DiGeorge syndrome (1pm, 2i) is a developmental error affecting the third and fourth pharyngeal pouches, derived from a 22q11 deletion. The thymus is hypoplastic and T-cell maturation is deficient.
- Features include:
    - Congenital heart disease
    - Abnormal facies
    - Thymic hypoplasia
    - Cleft palate
    - Hypocalcaemia

# What is severe combined immunodeficiency?

**Severe combined immunodeficiency (1pm, 2ow, 3i)**

- **The term is used for a variety of genetic syndromes which lead to defective humoural and cell-mediated immune function.**
- **Patients are vulnerable to a wide range of pathogens, including opportunistic infection.**
- **Treatment is normally via bone-marrow transplant.**

# Acquired Immune Deficiencies

# What is Acquired Immune Deficiency Syndrome?

- **Acquired Immune Deficiency Syndrome (1i)**
  - **Human immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS) is syndrome caused by infection with the human immunodeficiency virus (HIV).**

# How does HIV enter cells?

- The CD4 molecule has a high affinity for the HIV virus. HIV can potentially invade all CD4+ cells ($T_H$, macrophages, dendritic cells).
- A co-receptor is required for entrance. CCR5 is the coreceptor for R5 HIV strains (ca. 90% of initial infections); X4 strains bind to CXCR4, which is only expressed on activated T-cells.
- Upon entrance, the virus undergoes reverse transcription. It may remain latent for some time, but productive infection is stimulated by activation of the T-cell.

# What is the role of macrophages in HIV infection?

- Macrophages can harbor the HIV virus longer than CD4+ T-cells.
- Macrophages and monocytes transport HIV throughout the body and carry it into the nervous system.
- Even when CD4+ T-cells are severely diminished, viral replication continues in macrophages.
- HIV infected macrophages show impairment of phagocytosis, HLA II antigen expression and antigen-presenting capability, and increased production of IL-1, TNF, and IL-6.

# How does HIV deplete CD4+ (helper) T-cells?

- Infection of thymic progenitor and accessory cells leads to low production of mature T-cells.
- Apoptosis of uninfected T-cells (1pm) results from repeated activation by HIV antigens or other causes of infection.
- Lymphoid tissue architecture may be damaged by infection.
- HIV-specific CD8+ T-cells destroy infected CD4+ T-cells
- The HIV X-4 strain (1pm, 2i) causes syncytia (giant cell formation) between infected and uninfected cells, leading to cell death.

# What are the clinical manifestations of HIV?

## Clinical Manifestations of HIV (1i)

- **The characteristic presentation of AIDS includes fever, diarrhea, cachexia, lymphadenopathy, opportunistic infections, neoplasms, and neurological disorders.**
  - **Opportunistic infections (e.g., candida, CMV, tuberculosis, pneumocystic jiroveci pneumonia, toxoplasmosis)**
  - **Specific types of aggressive neoplasm (i.e., Kaposi's sarcoma, non-Hodgkin lymphoma.**
  - **Nervous system involvement (e.g., progressive encephalopathy ("AIDS dementia complex"), peripheral neuropathy, aseptic meningitis).**

# What are the main causes of iatrogenic immune compromise?

Iatrogenic immune compromise can result from:

1) Long-term/high dosage corticosteroid use.

2) Chemotherapeutic/radiation bone marrow suppression.

3) Therapeutic immunosuppression following organ transplants.

4) Treatment of auto-immune disease by means of immunosuppression .

# What are some common autoimmune diseases?

- **Systemic lupus erythematosus (SLE)**
- **Rheumatoid arthritis (RA)**
- **Ankylosing spondylitis**
- **Reactive arthritis (Reiter syndrome)**
- **Sjögren's syndrome**
- **Systemic sclerosis (Scleraderma)**
- **CREST syndrome**
- **Autoimmune  vasculitides**

# What are autoimmune diseases?

- Autoimmune diseases (1pm, 2pm, 3pm) are diseases stemming from defects in immunological self-tolerance.
- They may focus on one specific target (e.g., beta cells in type I diabetes) or be multisystemic (e.g., systemic lupus erythematosus).
- There is increasing evidence towards a strong genetic component of susceptibility to aut-immune disease (1pm).
- A list of many autoimmune diseases is available on Wikipedia.

# What is systemic lupus erythematosus (SLE)?

- Systemic lupus erythematosus (SLE) (1pm, 2pm, 3i, 4ow) is a complex autoimmune disease with a wide range of autoantibodies, including anti-nuclear, antiphospholipid, and anti-blood cell antibodies.
- It is comparatively common (possibly as high as 1:2500), with a 9:1 female:male ratio.
- SLE can affect any organ, but most often affects kidneys, skin, joints, and heart.
- The most common cause of death in SLE is renal failure.

# How does SLE cause renal damage?

- DNA/anti-DNA complexes and other products are deposited in the glomeruli (1pm, 2pm, 3pm).
- This leads to various characteristics of lupus nephritis, with inflammation and proliferation of epithelial and mesangial cells, and the characteristic “wire loops” (thickened peripheral capillary loops in the glomerulus (1i).
- Glomerular injury results in glomerulosclerosis and loss of kidney function.

# What renal lesions are characteristic of SLE (or found in SLE)?

- Glomerulonephritis (1pm)
  - Class I Minimal mesangial glomerulonephritis
  - Class II Mesangial proliferative glomerulonephritis
  - Class III Focal proliferative glomerulonephritis
  - Class IV Diffuse proliferative glomerulonephritis
  - Class V Membranous glomerulonephritis
  - Class VI Advanced sclerosing glomerulonephritis
- Tubulointerstitial inflammation
- Vasculopathy
- Thrombotic microangiopathy (usually in association with antiphospholipid antibodies)

# What is discoid lupus erythematosus?

- **Discoid lupus erythematosus (DLE) is an autoimmune disease that is largely limited to the skin and mucous membranes.**
- **Lesions typically located in the following areas:**
  - **Scalp**
  - **Bridge of the nose**
  - **Upper cheeks**
  - **Lower lip**
  - **Ears**
  - **Mucous membranes of mouth, nose, eye, or vulva,**

# What are cutaneous manifestations of lupus erythematosis?

- Malar rash (1i)
- Photosensitivity
- Subacute cutaneous lupus erythematosus (1i)
- Alopecia
- Lupus panniculitis (lupus profundus) (1i)
- Small vessel cutaneous leukocytoclastic vasculitis secondary to LE (1i)

- Discoid lupus (DLE)
- Localized DLE
- Generalized DLE
- Mucosal DLE
- (a) Oral DLE
- (b) Conjunctival DLE
- (c) Nasal DLE
- (d) Genital DLE (see pdf)
- Lichenoid DLE (LE/lichen planus
- overlap)

# How does SLE affect the central nervous system?

- The chief mechanism of SLE neurological damage is through angiopathy; but other antibody-mediated and cytokine neurotoxicities may contribute.
- Small vessel angiopathy is frequently seen, accompanied by ischaemia and/or multifocal microinfarcts.
- Antiphospholipid antibodies contribute to thrombosis, which may be the main factor leading to small vessel angiopathy (1pm, 2pm, 3pm).

# What role does small arterial vasculitis play in SLE?

- In lupus vasculitis (1ow), a combination of antibody, DNA, complement fragments, and fibrinogen is deposited in small artery/arteriole walls, leading to inflammation and necrosis
- Lupus vasculitis (1pm, 2pm, 3pm) may affect any organ or tissue.

# What are cardiac manifestations of SLE?

- Pericarditis: The serous membranes of the pericardium and pleura can show inflammation, which may lead to fibrosis (e.g., constrictive pericarditis).
- Myocarditis (1pm)
- Libman Sacks endocarditis
- Coronary artery disease

# What is rheumatoid arthritis?

- Rheumatoid arthritis is chronic autoimmune disease with both localized (joint erosion) and systemic manifestations.
- Prevalence is approximately 1%; female:male ratio is 3-5:1.
- Most commonly manifests in young to middle adulthood, but it may occur at any time of life.

# How does RA damage joints?

- The pathogenesis of rheumatoid arthritis has proven to be a complicated problem to unravel. It currently is believed to be an auto-immune disorder (1pm, 2pm, 3pm).
- T-cells are thought to be activated, producing pro-inflammatory cytokines and activating B-cells against joint self-antigens.
- TNF (tumour necrosis factor) is considered to be a crucial element.
- Chronic inflammation in the synovium leads to the formation of a pannus.

# What is an RA pannus?

- An RA pannus is a mixture of inflammatory cells, hyper-proliferative synovial lining cells, granulation tissue, and fibrous tissue.
- Articular cartilage and subarticular bone adjacent to the pannus are eroded.
- This produces the characteristic swelling, pain, bone deformity, and ultimately, via fibrosis and calcification, ankylosis.

# What are the radiographic findings indicating RA?

- Joint effusions
- Joint space narrowed (cartilage erosion)
- Juxto-articular osteopenia and erosion
- Other findings: swan-neck and boutonniere finger deformations, ulnar deviation ("windswept hand").

# What are the typical lab findings in RA?

- **Synovial fluid – sterile, loss of viscosity, turbid, with neutrophils containing inclusions.**

- **Positive rheumatoid factor.**

# What is rheumatoid factor (RF)?

- Rheumatoid factor (1pm) is an immune complex in which serum IgM (usually) or IgG autoantibodies bind to Fc region on self-IgG.
- RF is one of the components which can be deposited in joints or tissues and contribute to inflammation.
- RF only appears in ca. 80% of RA patients, so its absence does not rule out the presence of this disease.

# What are the systemic non-articular manifestations of RA?

- RA is an inflammatory process that can affect many organs and tissues. Affected sites have been extensively reviewed in the literature. The following are just two examples .
- Rheumatoid vasculitis - can lead to chronic leg ulcers, Raynaud's phenomenon (1i) (colour changes in extremities due to vascular spasming on exposure to temperature change), small nail infarcts, and rarely, gangrene of digits.
- Rheumatoid nodules (subcutaneous nodules – usually on areas subject to pressure, e.g. forearm extensor surface; can also form in organs and aorta). Painless, firm, up to 2 cm diameter. In a microscopic view of rheumatoid nodule , note a palisade of macrophages and central necrosis!

# What are some non-articular manifestations a rheumatoid arthritis?

- Non-articular manifestations of RA
  - Cutaneous lesions (small vessel vasculitis): splinter haemorrhages, periungual infarcts, leg ulcers, digital gangrene and sharply demarcated painful ulcerations.
  - Subcutaneous nodules (and histopathology): the upper forearm and elbow
  - Eye: keratoconjunctivitis sicca, episcleritis, scleritis, peripheral ulcerative keratitis --> corneal melt
  - Mouth: Oral dryness, salivary gland swelling,
  - Gastrointestinal: mesenteric vasculitis leading to intestinal infarction (rare)
  - Pulmonary manifestations: pleural effusions (with exsudative pericarditis), interstitial lung disease, pulmonary nodules.

# What are some more non-articular manifestations a rheumatoid arthritis?

- Non-articular manifestations (con't)
  - Cardiac manifestations: accelerated coronary atherosclerosis, pericarditis,, myocarditis, myocardial fibrosis and conduction defects, endocarditis with aortic or mitral valvular dysfunction, and arterial stiffness.
  - Renal manifestations (1pm), : mesangial glomerulonephritis, and amyloidosis and nephrotic syndrome.
  - Neurological: peripheral neuropathy, rheumatoid vasculitis syndrome, cervical myelopathy /atlantoaxial subluxation.
  - Haematolgical (ow): Felty's syndrome, multifactorial anaemia, neutropenia, thrombocytopenia, thrombocytosis, eosinophilia, and haematological malignancies, lymphadenopathy (benign follicular hyperplasia)

# How is rheumatoid arthritis treated?

- RA must be treated early and aggressively to avoid permanent deformation/loss of function.
- Mild cases can be treated with NSAIDs, corticosteroids, or Disease-Modifying Anti-Rheumatic Drugs (DMARDs) such as methotrexate.
- The most effective treatments are anti-TNF-$\alpha$ biologicals such as adalimumab, infliximab, and etanercept.

# What are seronegative spondylarthropathies?

- Seronegative spondylarthropathies are autoimmune diseases with several common characteristics.
- No rheumatoid factors detected (hence “seronegative”)
- Pathologies begin in ligaments rather than synovium
- Sacroiliac joint is commonly involved (ankylosing spondylitis)
- Associated with the HLA-B27 variant of the MHC I surface molecule.

# What are the major seronegative spondylarthropathies?

- Ankylosing spondylitis
- Reactive arthritis (Reiter's syndrome)
- Sjogren's syndrome
- Systemic sclerosis (scleroderma) (1pm, 2pm)
- Psoriatic arthritis

# What is ankylosing spondylitis?

- Ankylosing spondylitis is an autoimmune disorder characterized by:
- Chronic spinal joint inflammation, progressing to spinal joint fusion ("bamboo spine") and loss of torso mobility.
- Nonarticular manifestations can include uveitis (inflammation of the anterior chamber of the eye), cardiovascular abnormalities (aortitis, aortic insufficiency, pericarditis, myocarditis, AV blocks, and premature atherosclerosis). Upper lung fibrosis is also seen.
- Also associated with psoriasis and inflammatory bowel disease.
- The cause is not known. However, over 90% of sufferers display the HLA-B27 antigen.

# What is reactive arthritis?

- Reactive arthritis (Reiter syndrome) is a chronic autoimmune reaction to an infection.
- Most commonly provoked by GI infections (salmonella, campylobacter, shigella, yersinia).
- Can also be provoked by GU infections, particularly chlamydia.

# What are the symptoms of reactive arthritis?

- **Classic triad: uveitis, urethritis, and arthritis (asymmetric, oligoarticular lower-limb and sacroiliac arthritis)**
- **Other symptoms:**

  **Skin: keratoderma blenorrhagica, balanitis circinata**

  **Ulcers on tongue**

  **Cardiovascular: aortitis, aortic insufficiency, heart block**

# How is reactive arthritis treated?

- Treatment choice depends on severity and duration.

- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- Corticosteroids (joint injection)
- Corticosteroids (topical cream for skin rash)
- Disease-modifying anti-rheumatic drugs(DMARDs) (i.e., methotrexate or sulfasalazine)
- Biological anti-rheumatoid arthritis drugs (e.g., etanercept)

# What is Sjögren's syndrome?

- An autoimmune disease targeting exocrine gland ductal epithelial cells.
- It chiefly affects the salivary and lacrimal glands (dry eyes and dry mouth are the most characteristic clinical signs), but may affect any secretory glands.
- May be an autoimmune T-cell reaction against a specific glandular self-antigen or against a virus targeting these tissues.

# What are the symptoms of Sjögren's?

- Dry eyes – lead to erosion, ulceration, keratinization of the cornea.
- Dry mouth – caries, oral ulceration
- Dry nasopharynx – ulceration and erosion of nasal septum
- Dry respiratory tract – laryngitis, bronchitis, pneumonia
- Dry vagina – dyspareunia
- Ca. 25% of patients may also have extraglandular disease in muscles, skin, kidneys, and central nervous system.

# What other conditions are associated with Sjögren's?

- 61% of patients with other auto-immune disorders have Sjogren's syndrome – always remember that auto-immune diseases cluster, so the presence of one may lead to suspicion of others.

- Risk of lymphoma, particularly B-cell lymphoma, is increased significantly in Sjogren's. Much work is ongoing currently in regards to defining specific predictive factors.

# What is systemic sclerosis?

- Systemic sclerosis (1pm, also known as scleroderma – 95% of patients with this disorder develop skin involvement.
- Cause unknown but probably an auto-immune disease.
- Innate immune dysregulation may be key pathogenesis
- Self-activated CD4+ T-cells may activate mast cells and macrophages, which release fibrogenic cytokines.
- The result is excessive fibroblast activation and localized or generalized fibrosis.

# What systems are affected by systemic sclerosis?

- Cutaneous manifestations of scleroderma (follow links to images for details) – oedema followed by progressive dermal fibrosis and tight attachment to underlying structures. In late stages, blood supply may be compromised, causing ulceration and sometimes autoamputation of terminal phalanges. Most often noticed on face and hands.
- Gastrointestinal manifestations – atrophy of muscularis, replaced with collagenous fibrosis, especially in lower oesophagus. Dysfunction of lower oesophagal sphincter and gastric reflux. The small bowel may lose villi and microvilli, leading to malabsorption

# What systems are affected by systemic sclerosis – 2?

- Musculoskeletal (1pm)– synovial hyperplasia and inflammation. Inflammatory myositis in ca. 10% of patients.
- Pulmonary – over 50%. Pulmonary hypertension, interstitial fibrosis.
- Renal – ca. 2/3 of patients. Intimal cell proliferation in interlobular arteries. 30% of SS patients with kidney involvement develop hypertension; 20% of those develop hypertensive emergency, potentially leading to death.
- Cardiac (1pm) – myocardial fibrosis, intermyocardial arterial thickening.

# What is CREST syndrome?

- **Also known as "limited scleroderma" – mild skin involvement, viscera involved late if at all.**
- **CREST syndrome (1, 2, 3)=**
  - **Calcinosis (disseminated subcutaneous calcinosis) (1, 2, 3, 4)**
  - **Raynaud phenomenon (1)**
  - **Esophageal dysmotility**
  - **Sclerodactyly (1, 2, 3)**
  - **Telangiectasia (1, 2)**

# What are the autoimmune vasculitides?

- Autoimmune vasculitis encompass diseases in which autoimmunity leads to necrotizing inflammation of blood vessel walls.
- It is divided into 3 types of vasculitis:

1. Large-vessel (aorta and large branches to limbs, neck, and head)
2. Medium-vessel (visceral arteries and main branches)
3. Small-vessel (small arteries, arterioles, venules, capillaries)

# What are the large-vessel vasculitides?

- **Giant-cell arteritis (1pm, 2w)**

**- a granulomatous inflammation, usually affecting the temporal artery. Characterized by episodes of intense contact pain over the temporal area, pain upon mastication, often polymyalgia rheumatica. Typically seen in patients >50. Requires steroid treatment immediately to avoid risk of blindness!**

- **Takayasu's arteritis (1w)**

**- "pulseless disease" or "aortic arch syndrome". Granulomatous inflammation of the aorta leads to vascular insufficiency (hence "pulseless"), renal artery stenosis, and decreased blood supply to the brain. Typically first appears between 15 and 30 years of age.**

# What are the medium-vessel vasculitides?

- **Kawasaki disease**
- **Polyarteritis nodosa**

# What is Kawasaki disease?

- Kawasaki disease (1w) is suspected, but not proven yet, to be an auto-immune reaction.
- Most commonly seen in children < 5 years old.
- Inflammation of medium blood vessels throughout the body; lymphadenopathy of the neck, marked erythema of mucous membranes (notably the “strawberry tongue”).
- Can only be diagnosed clinically.

# What are the clinical characteristics of Kawasaki disease?

- **Five or more days of fever plus 4/5 diagnostic criteria:**

**1) Erythema and/or fissuring of the oral cavity and/or lips.**

**2) Truncal rash**

**3) Swelling or erythema of extremities**

**4) Conjunctival infection (red eyes)**

**5) Swollen lymph node (at least 1.5 cm) in neck.**

# What are potential consequences of Kawasaki disease?

- In the USA, 19 per 100,000 children <5yrs are hospitalized with Kawasaki disease every year
- #1 cause of childhood heart disease in US and Japan
- Cardiovascular complications include systemic aneurysms , coronary artery dilatation and/or aneurysms, pericarditis,, mitral regurgitation, aortic regurgitation.
- GI – intestinal obstruction, swelling, ischaemia
- Neurological complications (1% of cases)
- Eye changes – uveitis, ocular artery obstruction, conjunctival haemorrhage, optic neuritis

# What is polyarteritis nodosa?

- Polyarteritis nodosa was defined by the 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides as “a necrotizing arteritis not associated with antineutrophil cytoplasmic antibodies affecting  medium or small arteries but without glomerulonephritis or vasculitis in arterioles, capillaries, or venules”.

# What are the clinical features of polyarteritis nodosa?

- Polyarteritis nodosa is an autoimmune vasculitis chiefly affecting the medium to small arteries of the internal organs characterized by "rosary sign"; (the affected arteries may develop serial small aneurysms which resemble a string of beads).
- Strongly associated (ca. 30% of patients) with chronic hepatitis B.
- Both general systemic symptoms (fever, fatigue, weight loss) and organ-specific symptoms may be seen.
- Five year survival = 80% with treatment, 13% without.
- Treatment: immunosuppression (prednisone, cyclophosphamide); also treat underlying hepatitis B, if present.

# What are the small-vessel vasculitides?

- Granulomatosis with polyangiitis
- Churg-Strauss syndrome
- Microscopic polyangiitis
- Henoch-Schoenlein purpura

# What is granulomatosis with polyangiitis?

1) Granulomatosis with polyangiitis is “The Disease Formerly Known As ‘Wegener’s Granulomatosis’”.

2) It is an auto-immune granulomatous inflammation of the respiratory tract with small-vessel necrotizing vasculitis, most notably causing glomerulonephritis.

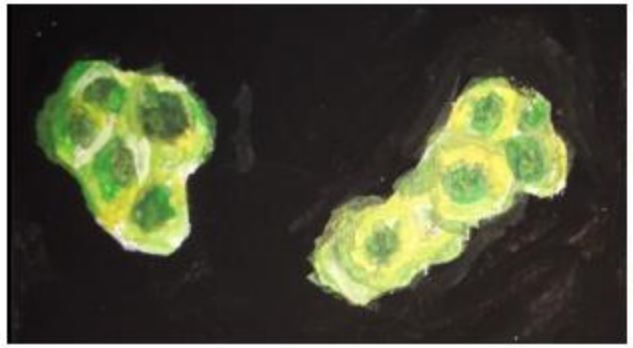
- The combination of kidney compromise plus pathologies of the nasopharynx and upper respiratory tract is the classical presentation.

- Particularly associated with c-ANCAs.

# What are c-ANCAs and p-ANCAs?

- ANCAs (anti-neutrophil cytoplasmic antibodies) are auto-antibodies targeting antigens in neutrophils.
- They are detected by immunofluorescence.
- C-ANCAs target granules throughout the neutrophil cytoplasm (hence “c”).
- P-ANCAs target antigens clustering around the nucleus of the neutrophil (“p” for “perinuclear”), chiefly myeloperoxidase.
- Both are strongly associated with small-vessel vasculitides.

C-ANCA under immunofluorescence shows a coarse granular pattern throughout the cytoplasm.



P-ANCA under immunofluorescence shows clustering around the nuclei and may cover the nuclei.

# What is Churg-Strauss syndrome?

- Churg-Strauss syndrome (1w, 2i) is a granulomatous and eosinophilic inflammation of the respiratory tract plus small-vessel necrotizing vasculitis.
- Associated with p-ANCAs and history of asthma/atopy.
- First presents with asthma and rhinitis, followed by eosinophilia and constitutional symptoms.
- Progresses to necrotizing vasculitis, which may compromise organs via reduced blood flow, clotting, and infarctions.
- Cardiac disease (eosinophilic pericarditis and myocarditis, compromise of coronary arteries) is the most severe complication.

# What is microscopic polyangiitis?

- Microscopic polyangiitis (1w, 2i) is a necrotizing small-vessel vasculitis.
- Can also lead to necrotic vasculitis in medium-sized arteries.
- Often presents with rapidly progressive glomerulonephritis and pulmonary capillaritis.
- Haematuria and proteinuria are common.
- Associated with p-ANCAs.

# What is Henoch-Schoenlein purpura?

- Henoch-Schönlein purpura (1w, 2i) is a vasculitis with deposition of IgA and IgA immune complexes in small vessels.
- Most commonly seen in children following an upper respiratory infection.
- Characterized by "classic triad":
  1. Purpura, largely on the lower torso and legs (always)
  2. Joint pain (80%)
  3. Abdominal pain (62%)

# What other systems are involved in Henoch-Schoenlein Purpura?

- Kidneys – ca. 40% of cases. Hematuria and proteinuria are common, loss of protein may lead to nephrotic syndrome. Progression to chronic kidney disease is seen in 1%.
- GI – haemorrhage, rarely intussuception.
- CNS and lungs are rarely involved.

# What infections most often lead to Henoch-Schoenlein Purpura?

- Streptococcus (β-haemolytic)
- Herpes simplex
- Adenovirus
- Coxsackie virus
- Measles
- Mumps

- And many others. Note that the most common provoking infections are common diseases of childhood!

# Can Henoch-Schoenlein Purpura be iatrogenically provoked?

**YES.**

**Drugs which have provoked Henoch-Schoenlein Purpura as an idiosyncratic reaction include:**

- **Vancomycin and cefuroxime (antibiotics)**
- **Enlapril and captopril (ACE inhibitors)**
- **Diclofenac (NSAID)**
- **Ranitidine (histamine H2 antagonist)**
- **Streptokinase (thrombolytic agent)**

# How is Henoch-Schoenlein Purpura treated?

- Analgesia as required for joint pain.
- Otherwise normally self-resolving.
- If kidney function deteriorates, a biopsy is taken to judge the need for immunosuppression.
- The degree of immunosuppression required depends on the condition of the kidneys, ranging from oral steroids to IV steroids and cyclophosphamide, plus dipyridamole to prevent blood clots and dilate vessels.

# Transplant and Graft Rejection

# What is the initial mechanism of graft rejection?

- Graft rejection (1w) stems initially from the recognition of foreign MHC molecules expressed by the donor cells.
- Donor dendritic cells express their own class II MHC molecules, triggering host CD4+ T-cells.
- The host's antigen-presenting cells process donor class I MHC molecules for presentation as foreign antigens.

# How do T-cells mediate rejection?

**Activated CD4+ T-cells produce a delayed-type hypersensitivity (hypersensitivity type IV; see Inflammation slide set) reaction. Recognition of MHC II donor antigens stimulates cytokine release, which leads to macrophage activation and injury to graft cells and vasculature.**

**CD8+ T-cells, stimulated by recognition of MHC I antigens, differentiate into cytotoxic (killer) T-cells and attack graft cells directly.**

# How do antibodies mediate rejection?

- **Antibodies to graft MHC molecules bind to graft endothelium, recruit leukocytes, and activate the complement system.**
- **Complement activation leads to platelet aggregation and coagulation, hence thrombosis.**
- **Hyperacute rejection occurs when preformed antidonor antibodies are already present: e.g., from previous transplants, transfusions, or pregnancies with Rh incompatibility.**

# How are rejection reactions classified?

- Hyperacute
- Acute cellular
- Acute humoral
- Chronic

# What are the characteristics of hyperacute rejection?

1) Time scale – minutes to hours.

2) Often recognized by surgeon immediately after completing vascular anastomosis – instead of regaining normal colour, turgor, and function, the organ rapidly becomes cyanotic and flaccid.

3) Histology – acute arteritis and arteriolitis, thrombosis, ischaemic necrosis. Arterial lumens are narrowed or occluded by precipitated fibrin; acute fibrinoid necrosis is seen.

# What are the characteristics of acute cellular rejection?

- 1) Time – days to weeks in a non-immunosuppressed patient, but can be months to years with immunosuppression.
- 2) Clinical signs of organ failure are present.
- 3) Histology – interstitial and inter-epithelial CD4+ and CD8+ infiltrates, oedema, possibly interstitial haemorrhage.
- Unless arteritis also occurs, an increase in immunosuppressive therapy is usually successful in halting the cellular rejection process.

# What are the characteristics of acute humoral rejection?

- 1) Timing – similar to acute cellular rejection

- 2) Necrotizing vasculitis (acute humoral rejection is also called rejection vasculitis).

  - Thickened intima, endothelial necrosis, antibody/complement/fibrin deposits, and thrombosis may all lead to infarction and ischaemic necrosis.

# What are the characteristics of chronic rejection?

- 1) Time – months to years after transplant.
- 2) Vascular changes and interstitial fibrosis, with slowly progressive dysfunction of the organ.
- 3) Increased proliferation of intimal smooth muscle cells and extracellular matrix compromise perfusion and lead to ischaemia.
- Chronic rejection is not treatable with standard immunosuppression.

# How are the chances of graft survival improved?

- HLA matching between donor and recipient (most notable when the two are closely related). Reduces the targeting of donor MHC molecules by host immune system.

- Immunosuppression – required in all cases except identical-twin donor/recipient pairs.

# How does immunosuppression work in transplants?

- Global immunosuppression was the original standard.
- Cyclosporine, tacrolimus, rapamycin, azathioprine, corticosteroids, anti-lymphocyte globulins, and monoclonal antibodies, among other drugs, are all used.
- However, creating an iatrogenic immunodeficiency carries its own hazards, similar to the problems of congenital or otherwise acquired immunodeficiencies.
- Belatacept, which blocks co-stimulatory signals on T-cell molecules, appears to be an effective and less-toxic alternative to cyclosporine or tacrolimus, but is still undergoing comparative evaluation.

# What are the special complications of bone-marrow transplants?

- Graft-versus-host disease (GVHD)
- Immunosuppression

# What is graft-versus-host-disease (GVHD)?

- Occurs when healthy immune system cells are transplanted into an immunocompromised patient.
- Usually seen with bone marrow transplants; may occur in transplanting solid organs with a high percentage of lymphoid cells.
- The recipient's compromised immune system cannot reject the graft; but grafted T-cells recognize the host tissue as alien.
- CD4+ and CD8+ donor T-cells are activated, creating both a delayed-type hypersensitivity and a cytotoxic lymphoid reaction.

# What happens in GVHD?

- Acute GVHD (days to weeks) causes epithelial necrosis in the liver, skin, and GI tract.
- Signs and symptoms:
  - Jaundice – from destruction of small bile ducts.
  - Generalized rash – cutaneous epithelial necrosis
  - Bloody diarrhea – mucosal ulcerations of the bowel.
- Chronic GVHD may follow a similar course, or may insidiously mimic systemic sclerosis or other autoimmune diseases.

# Why do bone marrow transplant patients suffer immunodeficiency?

- **The host immune system may have been suppressed or destroyed (e.g., by chemotherapy and/or radiation), both as direct therapy and to create an environment in which the graft may be successful.**

- **Full reconstitution is potentially a lengthy process. The patient may not be able to completely regenerate their immune system.**