Revise Nephrology Sydney
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Vasculitis and the Kidney

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Vasculitis- Inflamed vessel wall

- ***Inflammation of vessel walls causing damage to the walls***
- Clinical manifestations due to:
    - Vessel wall rupture- bleed
    - Luminal compromise- downstream ischemia/necrosis
- Often serious and sometimes fatal; immunosuppressive therapy can cause poor quality of life
- Classified depending on the size of the blood vessel involved
- Kidneys often involved- especially those effecting small vessels
- **Skin, joint, muscle, peripheral nerve, GI tract, lung and kidney commonly involved**

Vasculitis Classification

- *Large vessel vasculitis*

  Takayasu Arteritis

  Giant Cell Arteritis

- *Medium-sized vessels vasculitis*

  Polyarteritis Nodosa

  Kawasaki Disease

- *Small vessels vasculitis*

  Pauci-immune : Granulomatosis with polyangiitis (Wegener's)

  Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)

  Microscopic polyangiitis

  Immune complex-mediated: Cryoglobulinemic vasculitis

  IgA nephropathy/HSP

  Anti-glomerular basement membrane (anti-GBM) disease

  Hypocomplimentemic urticarial vasculitis (anti-C1q vasculitis)

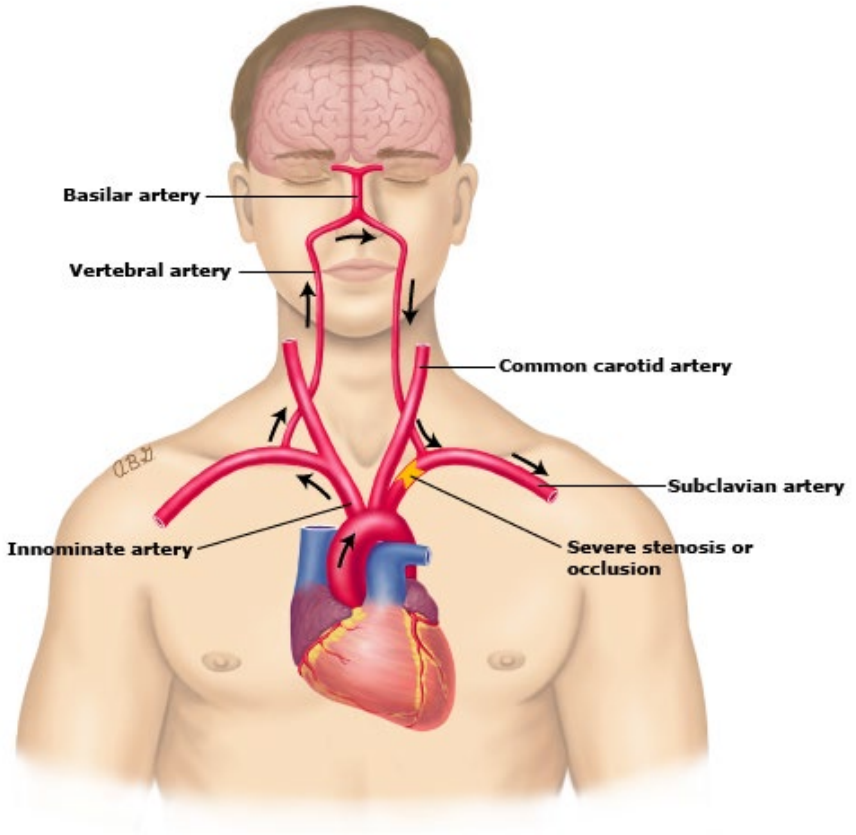
How is the kidney effected?

- Small vessel vasculitis- effect glomerular capillaries and thus lead to glomerulonephritis**……more exciting for the nephrologist…**
- Medium vessel vasculitis- Inflammation of interlobar/arcuate arteries causing thrombosis or rupture leading to renal infarction or haemorrhage respectively
- Large vessel vasculitis – effects aorta/main renal arteries leading to renovascular hypertension…..**almost like a renal artery stenosis….**

Takayasu Arteritis

- Primarily affects the aorta and its major branches
- Women affected in 80 to 90% of cases and Asians more effected
- Age of onset usually before 40 years of age
- Primarily granulomatous inflammation of aorta and its branches- initial proximal subclavian artery involvement common
- Abdominal aorta effected eventually in 50%
- Aneurysmal dilatation or scarred stenosed vessel
- **Renal involvement:** Involvement of the renal arteries leads to renovascular hypertension in > 50% cases

Takayasu Arteritis picture



American College of Rheumatology criterion

Needs 3 out of 6

- Age at disease onset ≤40 years
- Claudication of the extremities
- Decreased pulsation of one or both brachial arteries
- Difference of at least 10 mmHg in systolic blood pressure between the arms
- Bruit over one or both subclavian arteries or the abdominal aorta
- Arteriographic narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the proximal upper or lower extremities

NOTE- Angina and aortic regurgitation may be seen, fatigue, weight loss and low-grade fever common

Takayasu Arteritis

- Angiography/CTA/MRA helpful
- Mainstay of treatment is glucocorticoids
- 50% need steroid sparing agents like methotrexate, azathioprine etc.
- Sometimes for irreversible stenosis- percutaneous transluminal angioplasty or bypass grafts

Giant Cell Arteritis

As per American College of Rheumatology three positive out of following five criterion help to diagnose GCA:

- *Age greater than or equal to 50 years at time of disease onset*
- *Localized headache of new onset*
- *Tenderness or decreased pulse of the temporal artery*
- *Erythrocyte sedimentation rate (ESR) greater than 50 mm/hour*
- *Biopsy revealing a necrotizing arteritis with a predominance of mononuclear cells or a granulomatous process with multinucleated giant cells*

NOTE: Histologically Takayasu and GCA are similar

Polyarteritis Nodosa (PAN)

- Systemic vasculitis that typically affects medium-sized muscular arteries
- ANCA negative/ lung characteristically NOT involved
- Involvement of arterioles, veins and capillaries **excludes** PAN….so does GN exclude PAN? (yes)
- Aetiology unknown, 20-30% association with Hepatitis B
- Some association with Hepatitis C and Hairy cell leukemia
- Recessive loss of function mutations of the gene encoding adenosine deaminase 2 (ADA2)
- Pathology- segmental transmural fibrinoid necrosis of arteries accompanied by aneurysms and **no granulomas**

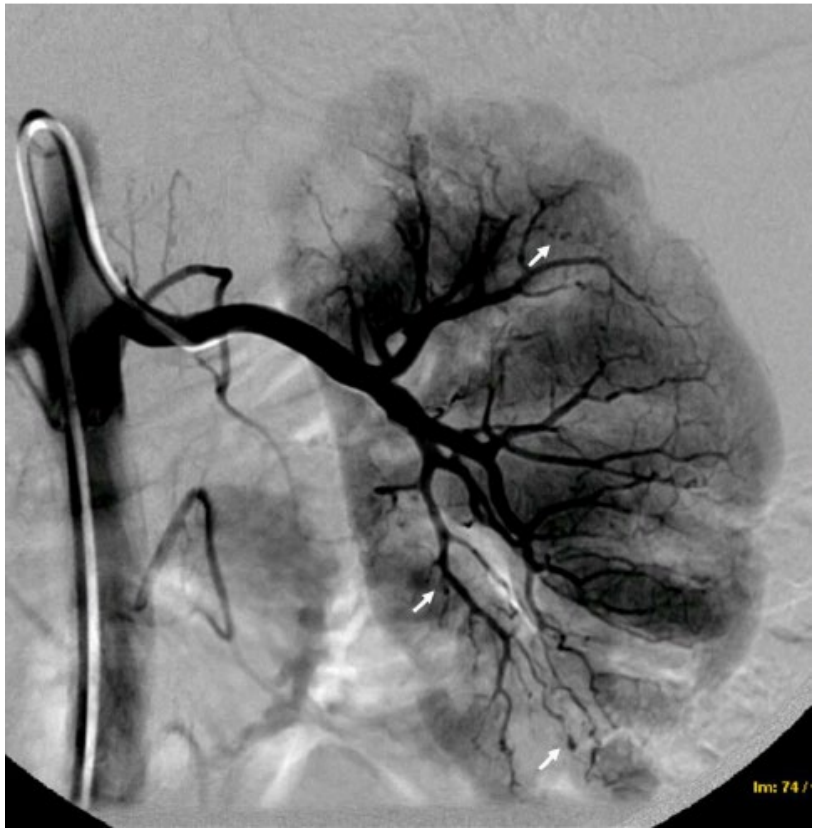
PAN presentation

Systemic features- fever/malaise	80%
Peripheral neuropathy	75%
Arthralgia/myalgia	60%
Skin- livedo reticularis,purpura	50%
Kidney- AKI due to infarct/bleed	50%
GI- abdominal pain, PR bleed	40%
Hypertension	35%
Orchitis	20%
Stroke	20%
Cardiomyopathy, pericarditis	10%

PAN diagnosis

- Biopsies of medium-sized vessels are not safe or practical and so uncommon
- **Mesenteric or renal arteriography is often diagnostic- multiple aneurysms and irregular constrictions in medium-sized vessels**
- *REMEMBER- No diagnostic laboratory test,no GN, no lung involvement, no ANCA, no involvement of arterioles/capillaries/veins and no granuloma on biopsy*

PAN- Multiple aneurysms and constrictions



PAN Treatment

- Depends on disease severity and presence/absence of hepatitis B
- **Mild disease-** arthritis, anemia, and skin lesions but NO renal, cardiac, GI, neurologic involvement: treat with prednisolone
- **Moderate to severe disease-** involvement of above or life-threatening complications…prednisolone and second immunosuppressive agent, typically cyclophosphamide initially followed by prednisolone and azathioprine for upto 18 months of total treatment
- **Hep B or C positive-** antiviral rather than immunosuppressive……..if severe PAN then short-term treatment with glucocorticoids and plasma exchange until antiviral therapy becomes effective….

ANCA Associated small vessel vasculitis

- Granulomatosis with polyangiitis (Wegener's previously):**90% ANCA +**[mostly PR3]
- Microscopic polyangiitis:**70% ANCA+** [mostly MPO]
- Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): **50% ANCA+** [MPO slightly > PR3]
- Renal-limited vasculitis — Pauci-immune vasculitis limited to the kidney with **75 to 80 % MPO-ANCA +**
- **Beware-**
  - 10-40% of Anti-GBM antibody disease ANCA+ [mostly MPO]
  - Drug-associated ANCA vasculitis: propylthiouracil, minocycline, hydralazine, cocaine contaminated with levamisole, penicillamine, clozapine and isoniazid

Q: What is ANCA??

Antineutrophil cytoplasmic antibody (ANCA)

- *Autoantibodies against antigens in the cytoplasm of neutrophils and monocytes*
- Two types of ANCA assays in wide use:

- Indirect immunofluorescence using alcohol-fixed buffy coat leukocytes (MORE SENSITIVE)

- Enzyme-linked immunosorbent (ELISA) using purified specific antigens (MORE SPECIFIC)

- Optimal approach: screen with immunofluorescence assays and if positive then confirm with ELISA

ANCA

- C-ANCA pattern: diffuse staining throughout cytoplasm with PR3 as the antigen most of the times
- P-ANCA: perinuclear pattern of staining (actually artefact of alcohol staining) with MPO as the usual antigen
- **Note**: False positive IF results for P-ANCA (e.g. in ulcerative colitis) could be due to other proteins e.g. lactoferrin, elastase, cathepsin G, bactericidal permeability inhibitor, catalase
- **Positive immunofluorescence ANCA should always be confirmed with the quantitative ELISA**

Overview of Pauciimmune Vasculitis

- *Preceded by fever, malaise, anorexia, and weight loss for weeks to months*
- Granulomatosis with polyangiitis (**(GPA)**- granulomatous inflammation effecting upper and lower respiratory tracts with GN (90% ANCA **+**[mostly PR3])
- Microscopic Polyangiitis **(MPO)**- Necrotising inflammation causing GN, pulmonary capillaritis but NO asthma/eosinophilia/granulomas (70% ANCA+ [mostly MPO])
- Churg-Strauss or Eosinophilic granulomatosis with polyangiitis **(EGPA)**- asthma, eosinophilia and necrotising granulomatous inflammation involving respiratory tract, renal involvement less common/severe (50% ANCA+ [MPO slightly > PR3])
- Prevalence is 2.5, 2.5 and 1/100000 respectively

Overview of Pauciimmune Vasculitis

- Some patients present with a renal-limited, ANCA-positive (75 to 80 percent MPO-ANCA) vasculitis
- Renal biopsy **(COMMON IN PAUCI-IMMUNE VASCULITIS);** segmental necrotizing glomerulonephritis often with crescents, no granulomas/**IF negative**

Granulomatosis with polyangiitis (GPA)

- **Lung and tracheal involvement in 90%-** pulmonary haemorrhage, nodular or cavitating lesions radiologically with tracheal or subglottic stenosis
- **ENT involvement in 90%-** sinusitis, rhinitis, subglottic stenosis, ocular inflammation, septal perforation and saddle nose deformity
- **Kidney involvement in 80%-** GN with/without proteinuria and renal failure, RPGN
- **Cutaneous manifestations** in 40%- leukocytoclastic angiitis causing purpura, ulceration and necrosis

Granulomatosis with polyangiitis (GPA)

- Less commonly- GIT, heart (pericarditis, myocarditis, conduction system abnormalities), neurologic system(asymmetric neuropathy, cranial nerve abnormalities, CNS mass lesion)
- **Diagnosis**- PR3 ANCA +v in 90%

  - CXR and CT Chest

  - Renal biopsy (COMMON IN ALL THREE PAUCI-IMMUNE VASCULITIS) shows segmental necrotizing glomerulonephritis often with crescents, no granulomas/**IF negative (pauciimmune GN)**

  - Nasal biopsy has high false negative rates, lung biopsy(open or thoracoscopic) may help in occasional patient with no renal involvement

Microscopic Polyangiitis

- **Kidney involvement in 80%-** GN with/without proteinuria and renal failure, RPGN
- Lung involvement in 40% , GI in 40%, ENT in 35% and neurologic system in 30%
- MPO/p-ANCA + in more than 80%
- Renal biopsy same as GPA…..but other site biopsy- NO GRANULOMA

Treatment of GPA and MPA

- IV methylprednisolone for 3 days followed by oral prednisolone at 1g/kg and Rituximab or Cyclophosphamide for induction(3-6 months)
- Remission in 85-90% in 3 months (75% achieve complete remission)
- Avacopan — Increasing use of this complement C5a receptor inhibitor as an adjunctive agent (avoid in those with active liver disease)
- Plasmapheresis: those needing dialysis, RPGN on biopsy, haemoptysis or concurrent anti-GBM disease
- Maintenance therapy with azathioprine/rituximab and low dose prednisolone usually given for 12 to 24 months *(remember PJP prophylaxis with co-trimoxazole)*
- Patients with PR3-ANCA are more likely to relapse than those with MPO-ANCA
- RAVE and RITUXIVAS trial established non-inferiority of rituximab as induction therapy vs cyclophosphamide
- MAINRITSAN trial showed superiority of rituximab over azathioprine for maintenance therapy

Efficacy of remission-induction regimens for ANCA-associated vasculitis' Specks U et al; N Engl J Med. 2013 Aug;369(5):417-27

PEXIVAS Trial (704 participants from 98 sites in 15 countries)

- Participants randomly assigned to 7 treatments of plasma exchange or no plasma exchange
- Standard-dose oral glucocorticoid regimen or a reduced-dose oral glucocorticoid regimen (<60% of the standard regimen by 6 months)
- Either cyclophosphamide (595-85% patients)or rituximab(109-15%)
- Followed for up to 7 years
- **Conclusion -Plasma exchange did not reduce ESRD or death**

-Lower rate of infections with low-dose steroids with non-inferiority compared to standard dose in regard to endpoint

Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis' Michael Walsh et al; February 13, 2020 N Engl J Med 2020; 382:622-631 DOI: 10.1056/NEJMoa1803537

Eosinophilic Granulomatosis with polyangiitis (EGPA or Churg-Strauss Syndrome)

- Characterised by asthma and eosinophilia with asthma preceding vasculitis by 8 to 10 years
- Mean age of diagnosis 50 years (GPA and MPA in older people)
- Develops in sequential phases with overlap at times-

  - *Prodromal phase* : In 2nd to 3rd decade with atopic disease/allergic rhinitis/asthma

  - *Eosinophilic phase*: pulmonary opacities, asthma, and peripheral eosinophilia with eosinophilic infiltration of lungs and GIT

  - *Vasculitic phase*: In 3rd to 4th decade with vascular/extravascular granulomatosis and fever, weight loss, malaise, and lassitude

- ENT involvement was reported in 70 to 85 % of patients

Diagnosis

- **As per Americal College of Rheumatology presence of four out of following six criterion is diagnostic-**
  - Asthma
  - Greater than 10 % eosinophils in blood
  - Mononeuropathy (including multiplex) or polyneuropathy
  - Migratory or transient pulmonary opacities detected radiographically
  - Paranasal sinus abnormality
  - Biopsy containing a blood vessel showing the accumulation of eosinophils in extravascular areas

Kidney involvement in about 50% cases and less severe than GPA or MPA

Cardiac involvement causes up to half of all deaths

Five-factor score (FFS)

- FFS, initially devised in 1996 , was revised in 2011:
  - Age >65
  - Cardiac insufficiency
  - Gastrointestinal involvement
  - Renal insufficiency (stabilized peak plasma creatinine concentration >1.7 mg/dL [150 micromol/L])
  - Absence of ENT manifestations (presence is associated with a better prognosis)
- Score of 0 is when none of the factors are present, a score of 1 for one factor, and a score of 2 for two or more factors.

Treatment of Churg-Strauss Syndrome

- IV Methylprednisolone for 3 days followed by prednisolone 1 to 1.5mg/kg daily leads to remission in > 90%
- Cyclophosphamide or rituximab added in cardiac/CNS/renal involvement or FFS= or >2
- Once remission achieved switch to azathioprine or methotrexate with prednisolone weaning for total duration of therapy for 12-18 months
- Non severe EGPA, treated with mepolizumab (interleukin 5 antagonist monoclonal antibody) and systemic glucocorticoids

Trumpisms .....

- "There's nothing I love more than women, but they're really a lot different than portrayed. They are far worse than men, far more aggressive, and boy, can they be smart!"

- Trump held a joint news conference with the emir of Kuwait, Sheikh Sabah Ahmed al-Sabah, who complained about media coverage in his country. Trump said, "I'm very, very honoured and happy to know that you have problems with the media also."

Thank you