

Chapter 27. Vasculitis

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Vasculitis is a multisystem disease caused by inflammation within the blood vessel wall, leading to disruption of the blood flow or damage to the vessel integrity.

It may affect one or many organ systems. The clinical features depend on the blood vessels involved. The common systemic features are fever, weight loss and generalised ill feeling.

Pathogenesis

There are three main ways in which the vasculitis damage can occur to the vessels.

- Direct damage by agent, example of this mechanism include;
 - Infection.
 - Cholesterol emboli.
 - Intravenous drug abuse.
- Antibodies directed at the vascular tissues. Anti endothelial cell antibodies are seen in conditions like Wegener`s Granulomatosis.
- Passive involvement of vascular tissue by inflammation, the typical example of this is serum sickness and essential mixed cryoglobulinaemia.

Epidemiology

Vasculitis is an uncommon collection of diseases. The estimated annual incidence rate vary between 2-9/1000,000 in the different syndrome that are described, and can even vary more widely, for example the incidence of polyarteritis nodosa in the general population in England is 4.6/1000,000 but in the hepatitis B infected population it reaches up to 77/1000,000.

The incidence of vasculitis is believed to be increasing partly due to the increased awareness of the condi-

tion and the wider use of the Anti-neutrophil cytoplasmic antibodies (ANCA) test.

Classic polyarteritis nodosa (PAN) affects men and women equally. Microscopic polyarteritis (MPA) is more common in males a ratio of 1.8:1. Polyarteritis is observed in children and the elderly but the average age at onset is about 50.

Classification of Vasculitis

The widely accepted classification of vasculitis is the Chapel Hill Consensus, which is based on the size of blood vessels involved

- *Large vessel*: (giant cell arteritis and Takayasu's disease). This category of vasculitis will not be covered in this chapter.
- *Medium vessel* (polyarteritis nodosa and Kawasaki's disease, which is mainly a paediatric disease and again not covered in this chapter)
- *Small vessel* (Wegener's, Churg-Strauss syndrome, microscopic polyarteritis, Henoch Schonlein purpura, cyoglobulinaemia and cutaneous vasculitis). The three main vasculitis syndromes, Wegener's, Churg-Strauss syndrome, microscopic polyarteritis will be discussed in this chapter.

Vasculitis can also be classified on the aetiological basis into:

- Primary (which includes the autoimmune vasculitis)
- Secondary
 - infection
 - malignancy
 - drugs
 - other autoimmune diseases

Clinical Features

Vasculitis may present in a variety of ways from mild self-limiting disease to rapidly progressive life threatening condition.

Almost all organs can be affected, typically patients present with constitutional symptoms of fever, weight loss and diffuse muscle aching along with the manifestations of multisystem involvement such as skin, peripheral nerves and visceral organs such as the gut, lungs and kidneys.

Skin

Includes palpable purpura, infarction, ulceration, livedo reticularis, subcutaneous nodules and ischemic changes of the fingertips, these features are present in around half of patients with PAN.

Musculoskeletal

Arthralgia and arthritis are present in about the same rate as the skin features in PAN, usually presenting early in the disease process as attacks of non-deforming, asymmetrical arthritis of large joints of the lower limbs.

Nervous System

Neuropathy affects more than half of PAN patients, present with mostly lower limb neuropathies. Central nervous system (CNS) vasculitis is much less common than peripheral nerve involvement, only around 10% of cases of PAN are affected and usually presenting with headaches, seizures or strokes.

Renal

Necrotising glomerulonephritis is a common feature of MPA and Wegener's Granulomatous. Classical PAN is usually characterised by vascular nephropathy leading to

multiple renal infarcts, renal failure and hypertension, renal angiography frequently show multiple micro aneurysms and infarcts.

Gastrointestinal

Abdominal pain, diarrhoea, gut haemorrhage and abnormal liver function tests are the common gut features in vasculitis, these can be the presenting symptoms or possibly a feature of recurrence of the disease even if they were absent at the initial onset. Abnormal liver function tests are especially common in classical PAN associated with HBs Ag positive patients.

Pulmonary

Pulmonary disease ranges from sub-clinical changes evident only on high resolution CT to life threatening pulmonary haemorrhage.

Asymptomatic pulmonary involvement is common. Haemoptysis and dyspnoea are the commonest clinical manifestations.

Alveolar shadowing on chest X-ray in the absence of the features of heart failure and infection is suggestive of alveolar haemorrhage.

Heart

Cardiac involvement although common pathologically is less often detected clinically, presenting with silent myocardial infarction or cardiomyopathy.

Specific Diagnostic Criteria Of Various Vasculitis Syndromes

Polyarteritis Nodosa And MPA

- Weight loss of > 4kg (not due to other causes)
- Livedoreticularis (mottled reticular pattern over the skin of the extremities)

- Testicular pain or tenderness (not due to infection or trauma and other causes)
- Myalgia
- Mono or polyneuropathy
- Diastolic BP >90mmHg
- Impaired renal function (urea>13mmol/l, creatinine>130mmol/l not due to other causes)
- Hepatitis B virus infection (HBs Ag or Ab positive)
- Angiographic abnormalities (angio showing aneurysms or occlusion of visceral arteries not due to atherosclerosis)
- Biopsy (showing granulocytes in the vessel wall)

Patient with vasculitis has PAN if 3 out of these 10 criteria are present with sensitivity of 82% and specificity of 88%.

The main distinguishing features of PAN are the presence of renal vasculitis, hypertension, micro aneurysms and HBV infection.

The main features of MPA include the rapidly progressive glomerulonephritis and lung involvement, which is usually absent in classical PAN.

Churg- Strauss Syndrome

- Asthma
- Eosinophilia > 10%.
- Mono or polyneuropathy
- Non-fixed pulmonary infiltrate.
- Para-nasal sinus abnormalities.
- Extra vascular Eosinophilia.

For classification purposes, a patient is said to have Churg- Strauss syndrome if 4 of these 6 criteria are positive with a sensitivity of 85% and a specificity of 99%.

Wegener's Granulomatous

The Chapel Hill consensus criteria suggests that a vasculitis patient has Wegener's Granulomatosis based on the presence of:

- Biopsy of tissue showing Granulomatosis in the respiratory system.
- Biopsy verified necrotising vasculitis in small to medium sized vessels or positive PR3-ANCA test.
- Lack of Eosinophilia in the blood and biopsy samples.

Wegener's Granulomatosis is typically manifested by recurrent sinusitis or epistaxis, mucosal ulceration, otitis media, cough, haemoptysis and dyspnoea. Destructive changes may lead to saddle nose deformity or tracheal stenosis. Eye involvement may take the form of episcleritis, uveitis and proptosis caused by orbital granuloma formation.

Behcet's Disease

The international study group for Behcet's disease has suggested the following criteria;

- Recurrent oral ulceration (not due other causes)
- Recurrent genital ulceration.
- Eye disease (uveitis or retinal vasculitis)
- Skin disease (erythema nodosum, pseudofolliculitis or pustular lesions)
- Pathergy sign (injecting a sterile saline in the skin of the patient results in the development of a sterile pustular lesion 48 hours later in the site of the injection)

A study of 519 cases of Behcet's disease in Tunisia confirmed the findings of other Mediterranean and Middle East countries, possibly also for the population of Libya, that positive Pathergy test and venous thrombosis were more common, where as ocular and neuro-

logical involvement were quite less frequent than the same disease presenting in other geographical areas. Venous thrombosis, uveitis and arterial involvement were significantly more common in males, where as erythema nodosum and joint disease were more frequent in females.

Investigations

- ESR and CRP are raised in cases of vasculitis.
- FBC may show anaemia of chronic illness and leucocytosis or Eosinophilia.
- Urinalysis – may show proteinuria, haematuria or red blood cell casts.
- Renal functions- impaired in cases of vasculitis with kidneys involvement
- Liver function tests- may be abnormal specially in PAN associated with hepatitis B virus infections
- ANCA test

The Diagnostic Value Of ANCA Test

ANCA test are widely used as a diagnostic marker for Wegener's Granulomatosis, microscopic polyarteritis, Churg Strauss syndrome and idiopathic rapidly progressive glomerulonephritis (IRPGN). The sensitivity of c (cytoplasmic)-ANCA is shown to be 64% in Wegener's Granulomatosis and 73% when combined with anti-proteinase 3 antibody. On the other hand the sensitivity of p (perinuclear)-ANCA in MPA is 58% and 67% when combined with anti-MPO (myeloperoxidase).

The specificity of these tests in combination i.e. (c-ANCA and anti proteinase 3) and (p- ANCA and myeloperoxidase antibody) is around 99% for Wegener's Granulomatosis, MPA, Churg Strauss syndrome and IRPGN. However in a significant number of patients with idiopathic vasculitis, ANCA test results are negative.

A study looked at the monitoring value of ANCA in 55 Wegener's Granulomatosis patients found that patients with persistent ANCA positive results after induction of remission with immune suppression or reappearing of positive ANCA later have much higher risk of developing clinical relapse compared to patients whose ANCA test remained negative. Therefore patients with positive ANCA test should be monitored more closely but treated in concordance with the clinical manifestations not on the basis of a positive test alone.

Tissue Biopsy

Skin biopsies: are minimally invasive procedures, when used appropriately can help to reach the correct diagnosis.

Kidney biopsy: to be performed if there is evidence of renal involvement by vasculitis (presence of red cell casts or proteinuria for example)

Sural nerve biopsy: Can be very useful if the vasculitis process involved the peripheral nerves.

Lung biopsy: Can either be done as an open lung biopsy or thoracoscopically.

Brain biopsy: Can be done to confirm CNS vasculitis, biopsy usually taken from the non-dominant hemisphere.

Electrophysiological Studies

- Nerve conduction studies are non-invasive procedures. It can be important in the diagnosis of peripheral nerve involvement in vasculitis.
- Electromyogram: it is a minimally invasive procedure that can help in detecting any muscular involvement due to the vasculitic process. Tissue biopsy can later be performed at areas of abnormal signals.

Angiograms

Angiograms of the gastrointestinal tract, renal artery or the CNS can be very useful in detecting the abnormal arterial micro-aneurysms and the beading in cases of CNS vasculitis.

CT scans

CT scans of different organs can detect the abnormal vasculitic process and possibly guiding the physician in directing the search for proper tissue diagnosis.

Management Of Vasculitis

The standard treatment of severe cases of vasculitis consists of oral cyclophosphamide in a dose of (2mg/ kg/ day) in combination with oral prednisolone (1mg/ kg/ day) to be reduced when the disease shows good response and for the cyclophosphamide to be continued for at least one year after complete remission is achieved. More recently pulses of cyclophosphamide and methyl-prednisilone have been used with very good results.

Azathioprine or methotrexate are used as maintenance treatment after induction of remission and possibly appropriate for the treatment of milder cases of vasculitis in combination with low doses of prednisolone.

Mycophenolate mofetil is a new medication that has shown very encouraging results in the induction and maintenance of remission in cases of severe vasculitis.

Intravenous Immunoglobulin was shown to be of some benefit in treating active vasculitis patients (for example reduce the incidence of coronary aneurysm in Kawasaki disease).

Plasmapheresis is mainly used for the acute cryoglobulinaemic crises.

Co-trimoxazole has been used in patients with limited (nasal) Wegener`s Granulomatosis.

The Definition Of Remission

Complete absence of any evidence of active disease proved by:

- Clearance of active lung lesions on Chest X -ray.
- Improvement or at least stability of renal functions.
- The absence of red cell renal casts in the urine sediment, proteinuria may continue.
- ESR returns to normal reading unless explained by other causes.

Medications Used In Behcet`s Disease

Low dose steroids were shown to be ineffective in controlling the orogenital ulceration or arthritic symptoms of behcet`s disease and therefore not indicated for the mild symptoms of the disease. Thalidomide is quite effective in treating the orogenital ulcers and follicular lesions but was noticed to increase the rate of erythema nodosa in these patients. Care must be taken to avoid the teratogenic effect of thalidomide.

Steroids in large doses are used to treat the eye complications of Behcet`s disease. Infliximab was shown to be effective in controlling the resistant cases of uveitis. Also, CAMPATH-1H (humanised ant CD52 A b) was found to be effective in achieving long lasting remission in the previously poorly controlled Behcet`s disease.

Differential diagnosis

The diagnosis of systemic vasculitis is based on combination of clinical, serological, histological and angiographic parameters. Syndromes that can mimic systemic vasculitis include:

- Atrial myxoma
- Bacterial endocarditis

- Cholesterol emboli
- Drug induced vasculitic process
- Thoracic outlet syndrome
- Hypertensive angitis
- Goodpasture`s syndrome

It is important to exclude these conditions and reach to a reasonable level of diagnostic accurately before initiating the immune suppressive therapy for vasculitis.

Prognosis

The outcome of vasculitis is dependent upon the extent of visceral organ involvement. Most of deaths happen in the first year of disease due to delayed diagnosis, superimposed infections or treatment complications. The 5-year survival of untreated polyarteritis is 15%, which has improved with the use of steroids and cyclophosphamide to 80%. Bad prognostic features include:

- Over 50 years old at presentation
- More than 1 gram/ day of proteinuria
- Renal insufficiency at presentation
- Cardiac, gastrointestinal tract or CNS involvement
- Co-morbid conditions like diabetes and cerebrovascular disease increase the mortality of vasculitis patients.
- High ESR at presentation is a good marker of disease severity.

The commonest cause of death in Wegener`s Granulomatosis patients is pulmonary haemorrhage followed by pneumocystis carini infection. Ear, nose and throat involvement in Wegener`s Granulomatosis indicated better prognostic outcome. The presence of mononeuritis multiplex does not affect the mortality rate.

Relapses in vasculitis syndromes are quite common. During a 10 years period of observation, around 40% of

cases of PAN relapsed with a median time to relapse of about 30 months.

The effectiveness of vasculitis management could be improved by the appropriate choice of therapy as guided by the presence or absence of bad prognostic factors.

Further Reading

1. Thickett DR. Pulmonary manifestations of ANCA positive vasculitis. *Rheumatology* 2006;45:261-268.
2. Moayer MF Churg-Strauss- syndrome updates. Jan 2007; *E medicine*.
3. Sharma S Wegener's G Granulomatosis updates. May 2006; *E medicine*.
4. Seo JH Sensory neuropathy in vasculitis: a clinical, pathologic and electrophysiological study. *Neurology* 2004;63:874-878.
5. Langford CA. Vasculitis. *Allergy clinical immunology* 2003; 111(suppl):S602-S612.
6. Wilk A. Rational use of ANCA in the diagnosis of vasculitis. *Rheumatology* 2002;41:481-483.
7. Girard T. Are ANCA a marker predictive of relapse in WG? A prospective study. *Rheumatology* 2001;40:147-151.
8. Barnes CG. Treatment of Behcet's Disease. *Rheumatology* 2006;45:245-247.
9. Hamzouaoui B. Behcet's disease in Tunisia. Clinical study of 519 cases. *Rev Med Interne* 2006;27: 742-750.
10. Guillevin L, Lhote F, Gayraud M, et al. Prognostic factors in Polyarteritis nodosa and Churg-Strauss syndrome in 342 cases. *Medicine (Baltimore)* 1996; 75:17-28.
11. Maher A. Analysis of factors predictive of survival based on 49 patients of Wegener's Granulomatosis and prospective follow up. *Rheumatology* 2001;40:492-498.
12. Exley AR. Clinical disease activity in vasculitis. *Current opinion rheumatology* 1996;8:12-18.
13. Cruz BA. Prognosis and outcome of 26 patients with systemic necrotising vasculitis admitted to the ICU. *Rheumatology* 2003;42:1183-1188.

14. Garcia P. Polyarteritis nodosa and mixed cryoglobulinaemia related to hep B and C viruses' co infection. Annul rheum 2001;60:1068-1069.

Websites

1. WWW.VASCULITIS.ORG
John KLippel, Paul Dieppe text book of rheumatology.